TRATTAMENTO DEL PAZIENTE CON MIELOMA MULTIPLO AD ALTO RISCHIO ALLA RICADUTA

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MULTIPLE MYELOMA: CHANGING THE PARADIGM IN RRMM

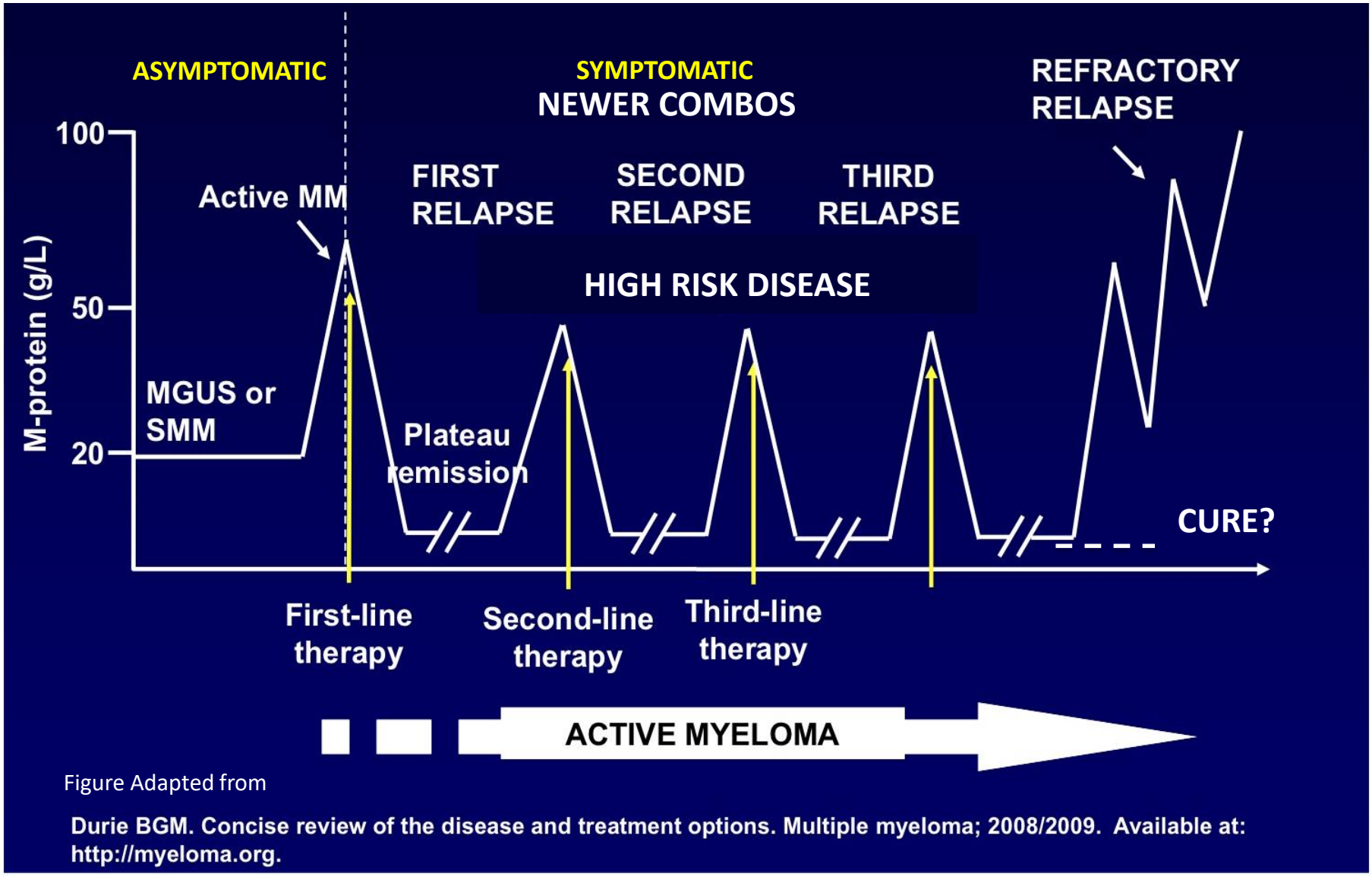
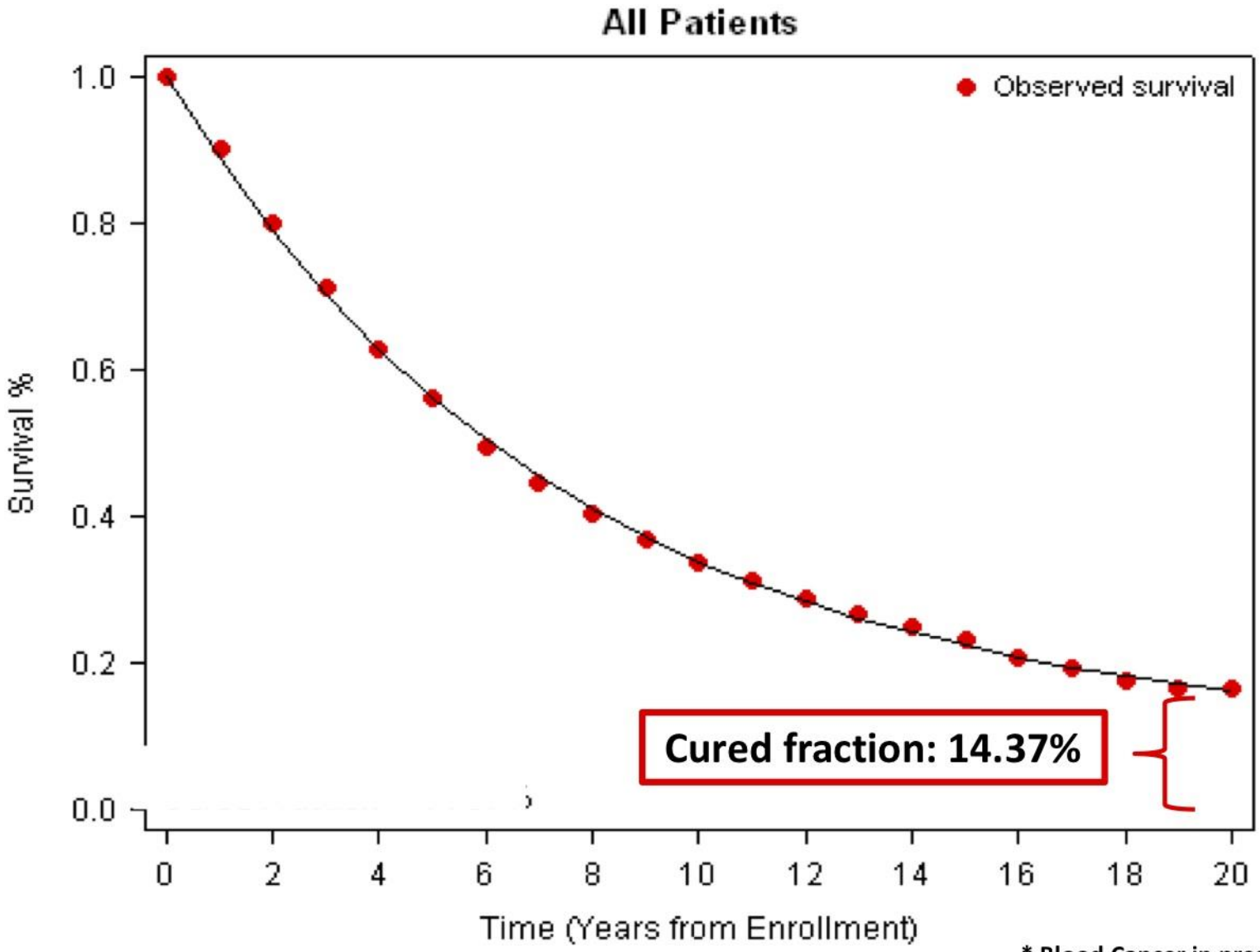


Figure Adapted from

Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009. Available at: http://myeloma.org.

MULTIPLE MYELOMA: "CURE FRACTION" FROM IMWG ANALYSES*



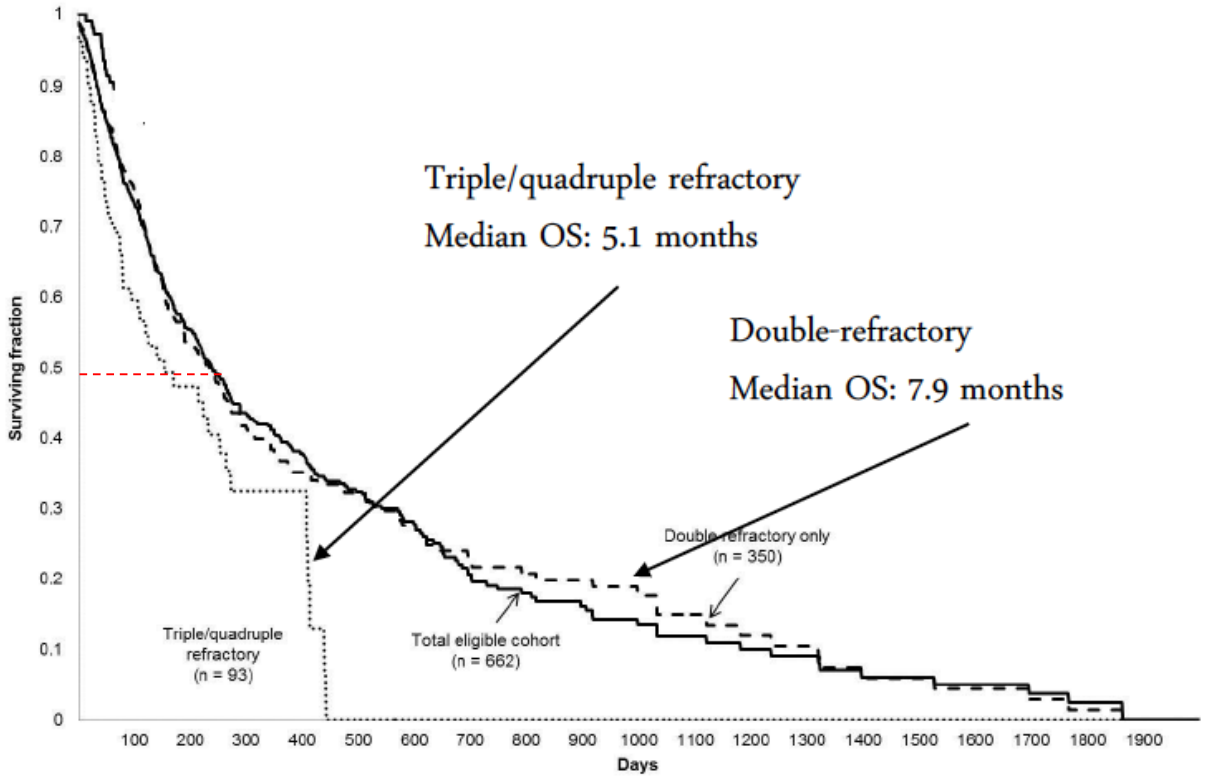
* Blood Cancer in press 2018

RELAPSED AND REFRACTORY MM: OS

Despite the introduction of IMiDs and PIs, most patients relapse and outcomes are poor in relapsed or refractory patients[1]

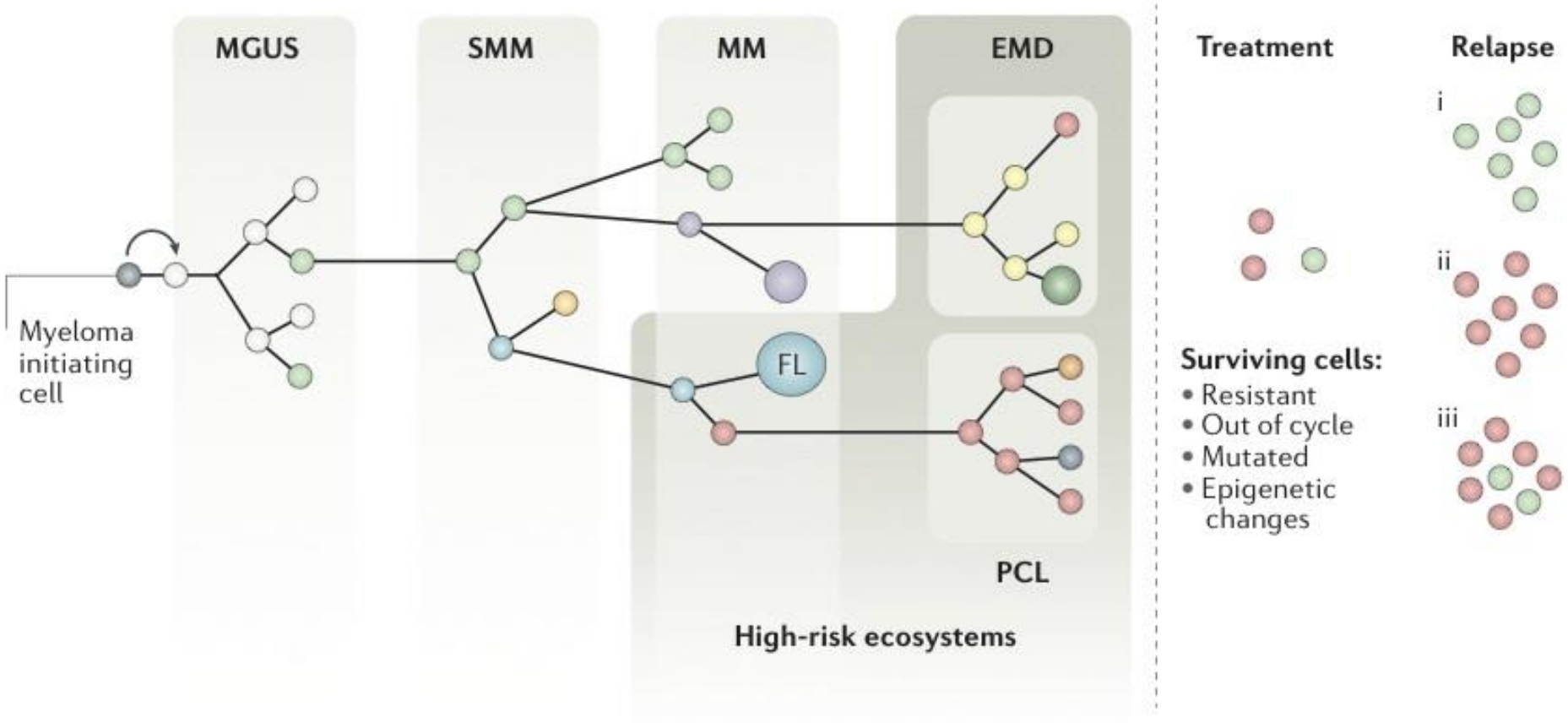
Median OS of 9 months in patients refractory to bortezomib and at least one IMiD[1]

Median OS of 7.8 months in patients with relapsed or refractory MM who were double refractory or 5.1 months for those who had relapsed after ≥3 prior lines of therapy, and were triple/quadruple refractory, including pomalidomide and carfilzomib[2]



1. Kumar SK, et al. Leukemia 2012
2. Usmani S, et al. Presented at ASH 2015; abstract 4498

MYELOMA CLONAL EVOLUTION TO HIGH RISK



…the high-risk biological states of multiple myeloma are the end stage of a multi-step progression system characteristic of the disease…

Pawlyn C and Morgan GJ Nature Reviews Cancer 2017

NOT ALL RELAPSES IN MM ARE THE SAME

Aggressive		Non Aggressive
Short duration of response or progression while on therapy	Timing of relapse	Long duration of response
Sharp rise (doubling time < 2 months)	Speed of M protein rise	Gradual rise over several months
Rapid onset Hypercalcemia Severe anemia Acute renal failure Skeletal-related events	CRAB criteria	Slow onset Minimal complication
Extramedullary disease PCL, High LDH Adverse cytogenetic abnormalities ISS stage II/III at relapse Light chain escape	Other factors	No extramedullary disease LDH in normal range No PCL

Adapted from Sonneveld P Hematology 2017

PROGNOSTIC FACTORS IN RELAPSED MM

TUMOR CELL RELATED

- Ploidy (hyperdiploidy vs hypodiploidy)
- Translocation
  - t(4;14)
  - t(6;14)
  - t(11;14)
  - t(14;16)
  - t(14;20)
- Monosomy 13 (by citogenetics)
- 17p deletion (or loss of *TP*53)
- 1q amplification
- 1p-
- Complex karyotypes
- Lactate dehydrogenase (above normal)
- Circulating plasma cells (any number)
- Plasma cell growth rate (>3% by flow cytometry)
- Gene expression profile (various platforms)

TUMOR BURDEN

- Durie-Salmon stage
- International Staging System
- Extramedullary disease

PATIENT RELATED

- Age
- Performance status
- Renal failure
- Frailty (IMWG guidelines)

Dingli D et *al* Mayo Clin Proc 2017

SMART RISK CLASSIFICATION IN RELAPSED MM

HIGH RISK	INTERMEDIATE RISK	STANDARD RISK
• Primary refractory disease • Relapse < 12 months from ASCT • Progression within the first year of diagnosis • **FISH** - Deletion 17p - t(14;16) - t(14;20) • High risk GEP	• FISH - t(4;14) - 1q amp • High "S" phase	All others including - Trisomies - t(11;14) - t(6;14)

MSMART: Mayo Stratification for Myeloma and Risk-Adapted Therapy.

Dingli D et *al* Mayo Clin Proc 2017

SUMMARY OF CYTOGENETIC RISK FEATURES

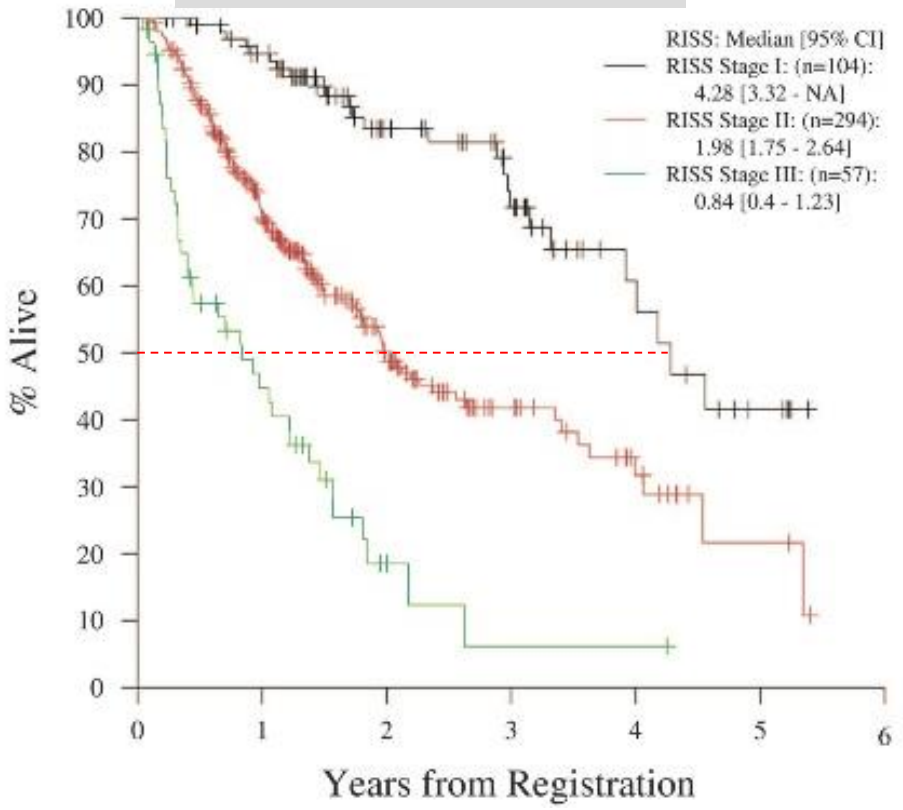
	High-risk	Standard-risk
Cytogenetic abnormality	FISH: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q) Non hyperdiploid Karyotipe Karyotype del(13) GEP: high-risk signature	All others including: FISH: t(11;14), t(6;14)

- Cytogenetic **abnormalities by FISH** currently are clinically relevant prognostic factors in MM.
- The IMWG consensus panel on FISH advises to test for the presence of **del(17p), t(4;14), and possibly t(14;16).**
- An extended panel, which may be incorporated in clinical trials, includes t(11;14), t(14;20), gain(1q), del(1p), del(13q), and ploidy status.

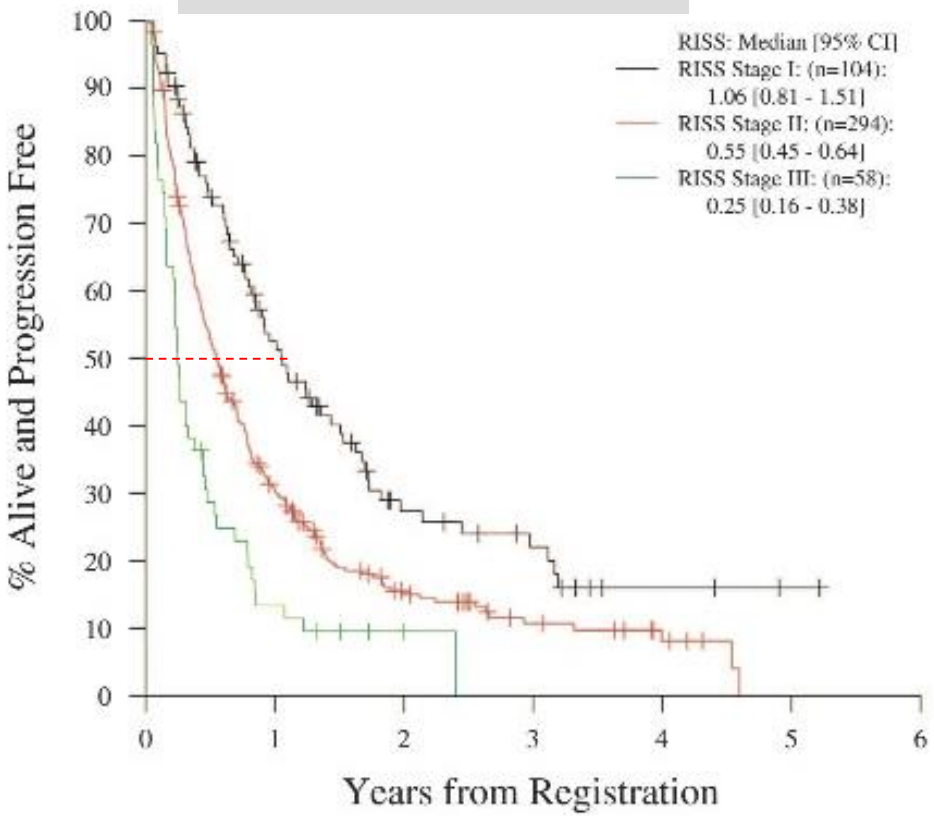
Sonneveld P *et al* Blood 2016

OS and PFS for DIFFERENT R-ISS STAGES AMONG PATIENTS with RRMM

OS relapsed patients



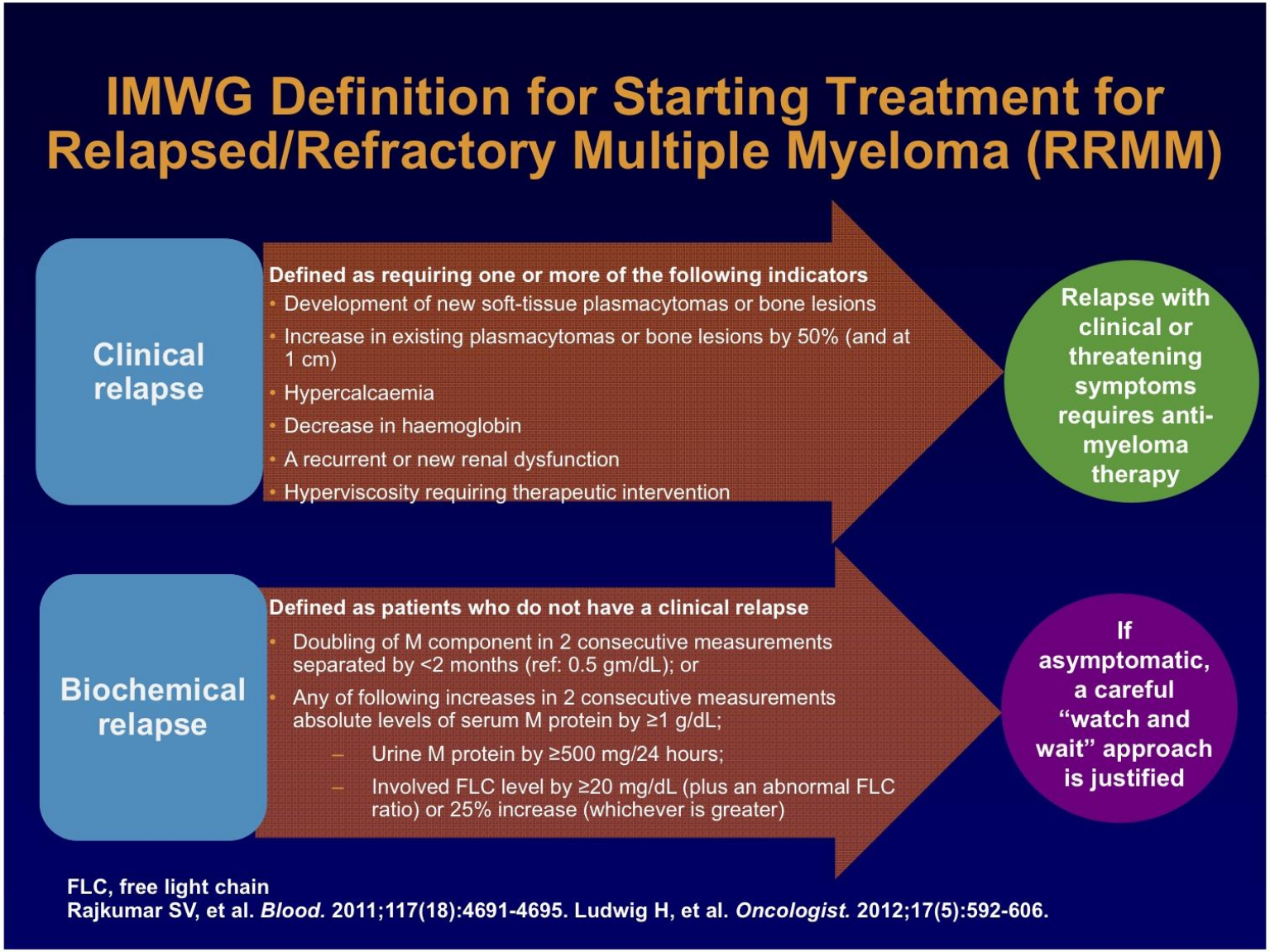
PFS relapsed patients



Diagnostic Test	*Cohort*	*Median OS years*	*Median PFS years*
RISS	RISS-I	4.28 (3.32–NA)	1.06 (0.81–1.51)
	RISS-II	1.98 (1.75–2.64)	0.55 (0.45–0.64)
	RISS-III	0.83 (0.40–1.23)	0.25 (0.16–0.38)
	Total	2.37 (1.96–3.15)	0.60 (0.49–0.70)

Tandon N et *al* Blood Cancer Journal 2017

WHEN TO START TREATMENT



BIOCHEMICAL RELAPSE: WHEN to START TREATMENT

It is reasonable to initiate salvage regimens before the development of symptoms, particularly if:

- THERE IS STEEP INCREMENT IN M SPIKE
- **HIGH RISK RELAPSED DISEASE** Table 1. LAUBACH J *et al LEUKEMIA 2016*

THE DEFINITION OF HIGH-RISK IS ALSO DYNAMIC, CHANGING OVER TIME!

Disease related parameters	
Adverse cytogenetic abnormalities	del(17p), amp(1q21) or t(4;14)
Extramedullary disease	
Short remission duration after first treatment	
ISS stage at relapse	
Isotype transformation	Light chain escape, development of hyposecretory disease
High LDH levels at relapse	

Laubach J *et al* Leukemia 2016 **Table 1.**

CHOOSING THERAPY FOR THE MANAGEMENT OF MM R/R

Myeloma-related factors

- Rapid increase in tumor burden/bone lesions
- Extramedullary disease
- Plasma cell leukemia
- Elevated LDH
- ISS III disease at relapse
- High-risk cytogenetics

Previous Therapy

- ASCT
- IMiD-based or PI- based
- Maintenance

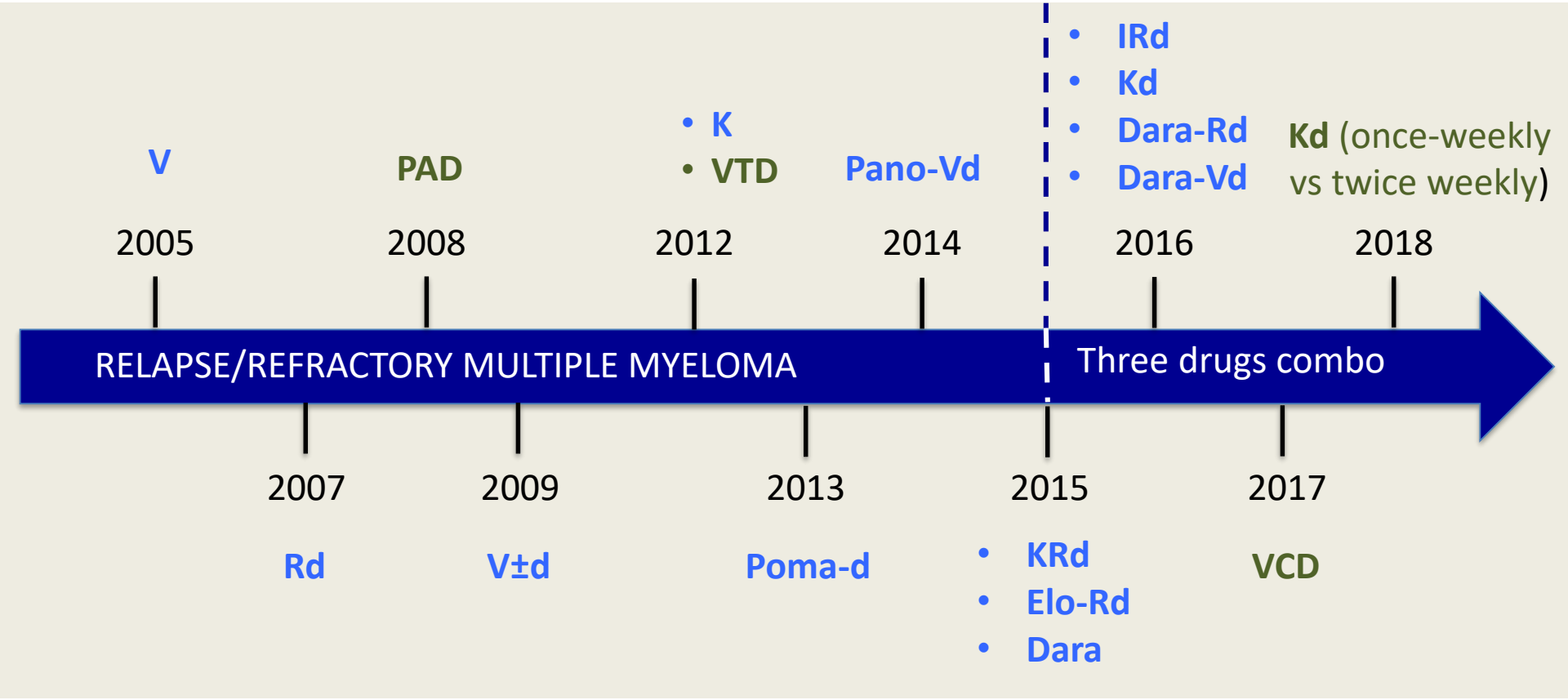
Patient-related factors

- *Frailty due to age or multiple comorbidities (20% SAE in many relapse trial)
- Renal impairment
- Cardiac disfunction
- Peripheral neuropathy
- Bone marrow reserve
- Transplant elegibility
- Expectations of the patient
- Oral vs IV
- Support network

Therapy-related factors

- Sensitivity to previous therapy
- (Response, TFI, PFS)
- *Toxicity to previous treatments (Frailty)
- Availability, cost and management requirements
- Availability of clinical trial
- Local guidelines

TIMELINE OF KEY AGENTS AND TREATMENT COMBINATIONS



Approved by FDA/EMA

Recommended in current European/US treatment guidelines

Adapted from Costello C e*t al* Future Oncology 2019

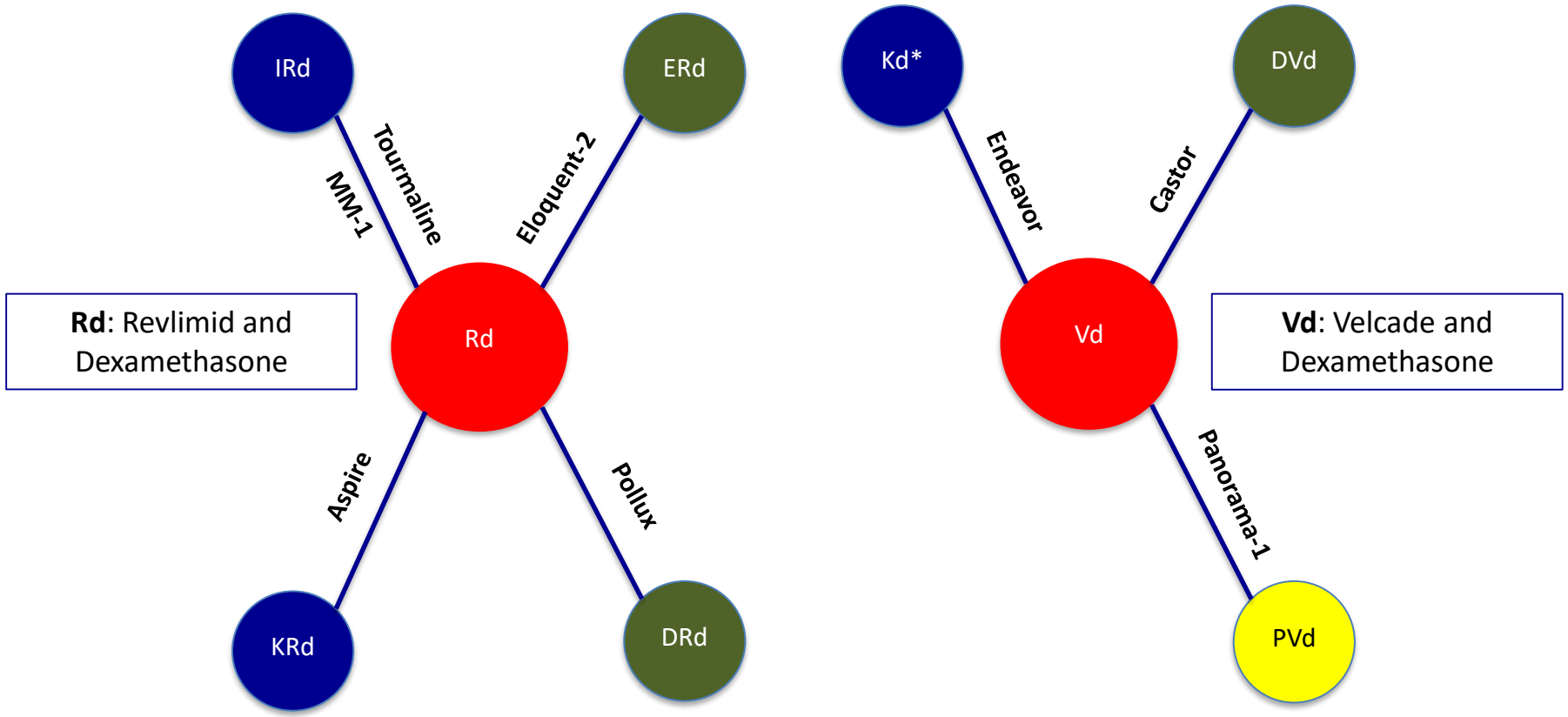
RECENTLY APPROVED DRUGS AND PHASE III STUDIES in RRMM

- Carfilzomib (K)
- Ixazomib (I)
- Daratumumab (D)
- Elotuzumab (E)

- Panobinostat (P)
- Daratumumab (D)
- Carfilzomib (K)

New Drug plus Rd vs. Rd

New Drug plus Vd (or d*) vs. Vd

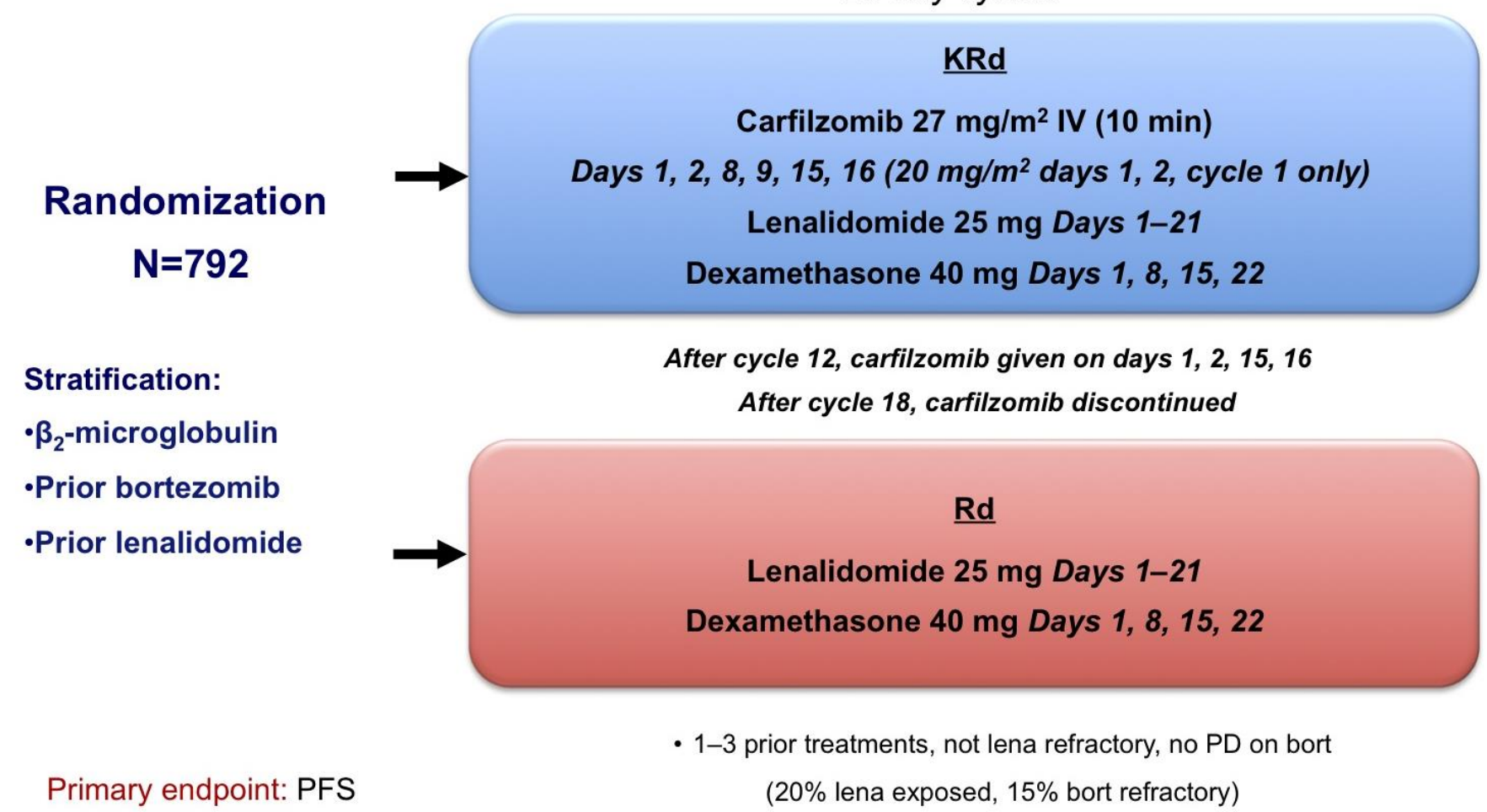


Rd: Revlimid and Dexamethasone

Vd: Velcade and Dexamethasone

ASPIRE: Carfilzomib, Revlimid and Dexamethasone (KRd) vs Revlimid and Dexamethasone (Rd) in RRMM

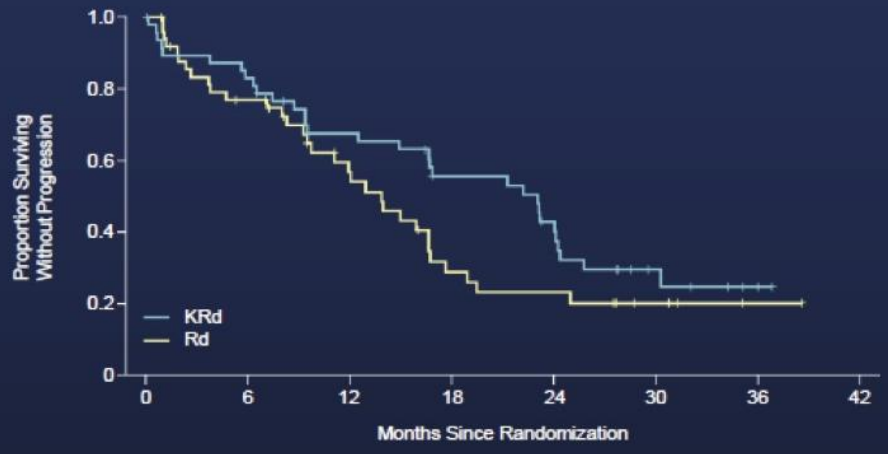
Carfilzomib is approved by FDA and EMA in combination with len-dex for pts who have received at least 1 prior line of therapy



Stewart K et al, NEJM 2015

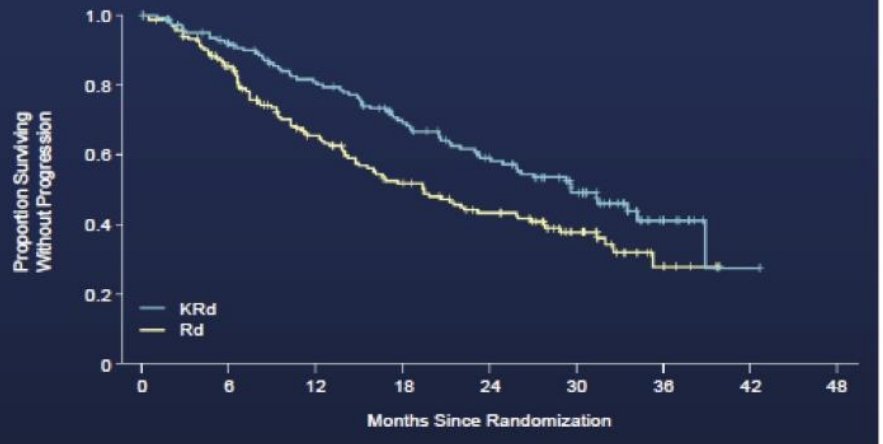
ASPIRE: PFS BY CYTOGENETIC RISK STATUS AT BASELINE

High Risk



	KRd (n=48)	Rd (n=52)
PFS, median months	23.1	13.9
Hazard ratio (95% CI)	0.703 (0.426–1.160)	
P-value (1-sided)	0.0829	

Standard Risk



	KRd (n=147)	Rd (n=170)
PFS, median months	29.6	19.5
Hazard ratio (95% CI)	0.656 (0.480–0.897)	
P-value (1-sided)	0.0039	

- KRd effective in patients with t(4;14 and del (17/17p)
- High risk defined by: t(4;14) or t(14;16) or with del(17p) in ≥60% of PCs

CI, confidence interval; KRd, carfilzomib, lenalidomide, and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

Avet Loiseau H et al. Blood 2016;128(9):1174–118

TOURMALINE-MM1: Ixazomib, Revlimid and Dexamethasone (IRd) vs Revlimid and Dexamethasone (Rd) in RRMM

Ixazomib is approved by FDA and conditionally approved by EMA in combination with lenalidomide-dexamethasone for patients who have received at least 1 prior therapy

Global, double-blind, randomized, placebo-controlled study design

N=722

Randomization

1:1

Ixazomib + Lenalidomide + Dexamethasone
Ixazomib: 4 mg on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

Placebo + Lenalidomide + Dexamethasone
Placebo: on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

Primary endpoint:
- PFS

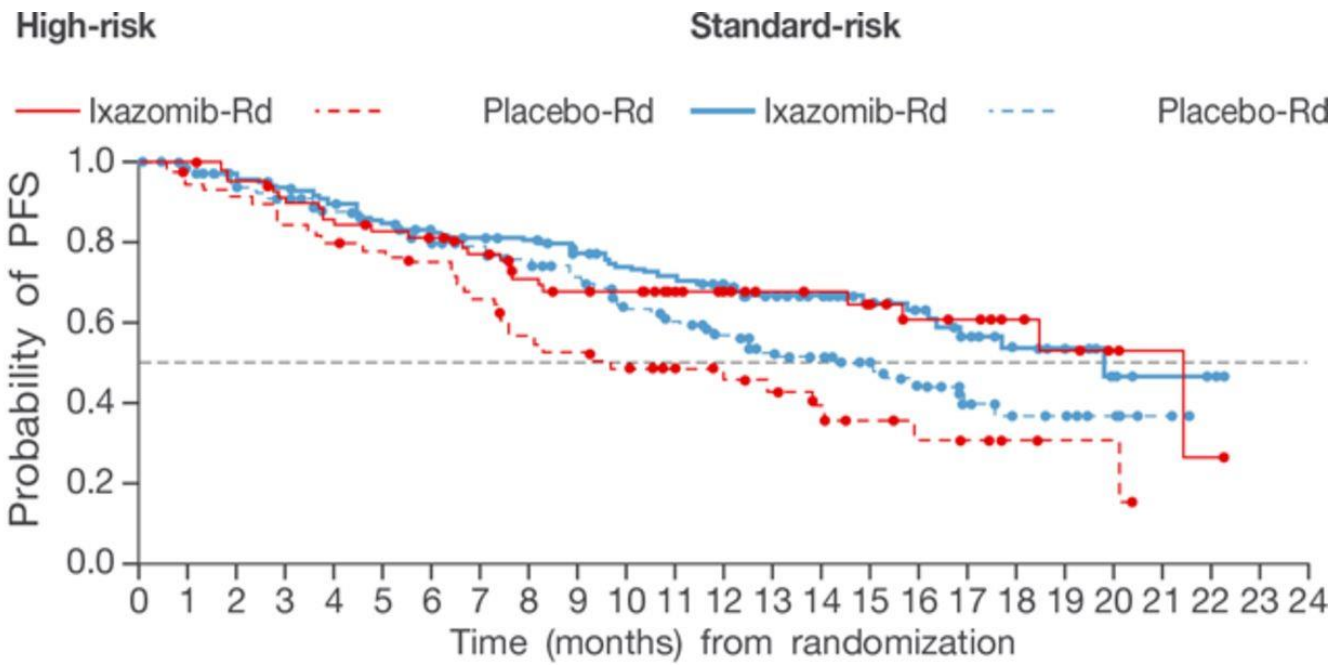
Key secondary endpoints:
- OS
- OS in patients with del(17p)

- Received 1–3 prior treatments
- Not refractory to len or bort
- 70% bort exposed, 12% lena exposed

including primary refractory patients

Moreau P et al. NEJM 2016

TOURMALINE-MM1: PFS BY CYTOGENETIC RISK STATUS AT BASELINE



Patients by Cytogenetic Status	Median PFS, mo		HR
	IRd	Placebo/Rd	
All (N = 722)	20.6	14.7	0.742
Standard risk (n = 145)	20.6	15.6	0.640
High risk (n = 137)	21.4	9.7	0.543
Del(17p)[a]	21.4	9.7	0.596
t(4;14) alone (n = 61)	18.5	12.0	0.645

[a] Alone or in combination with t(4;14) and/or t(14;16).

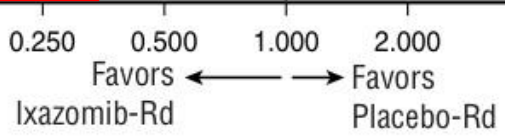
1. Richardson PG et al. ASCO 2016. Abstract 8018.

Avet-Loiseau H, *et al.* Blood 2017

TOURMALINE-MM1: PFS BY CYTOGENETIC RISK GROUP

Forest Plot of PFS in IRd and Placebo-Rd groups among patient subgroups defined by citogenetic abnormalities, including post-hoc analyses of different cut-off values for individual abnormalities

Variable	Subgroup	n/N (events/pts) Ixazomib-Rd	n/N (events/pts) Placebo-Rd	Median PFS (months) Ixazomib-Rd	Median PFS (months) Placebo Rd	HR (95% CI)
All patients	ALL	129/360	157/362	20.6	14.7	0.742 (0.587–0.939)
Cytogenetic risk	High-risk	26/75	35/62	21.4	9.7	0.543 (0.321–0.918)
	Expanded high-risk	62/155	83/154	17.5	11.1	0.664 (0.474–0.928)
	Standard-risk	61/199	91/216	20.6	15.6	0.640 (0.462–0.888)
del(17p)*	Positive (5%)	14/36	20/33	21.4	9.7	0.596 (0.286–1.243)
	Positive (20%)	13/29	19/30	21.4	6.7	0.611 (0.286–1.308)
	Positive (60%)	10/19	8/14	15.7	5.1	0.490 (0.146–1.644)
t(4;14)*	Positive (3%)	11/36	11/25	18.5	12.0	0.645 (0.250–1.663)
	Positive (20%)	11/36	10/22	18.5	12.0	0.685 (0.259–1.811)
	Positive (60%)	8/25	8/15	18.5	9.3	0.518 (0.166–1.615)
Amp 1q21*	Positive (3%)	36/80	48/92	15.4	11.3	0.781 (0.492–1.240)
	Positive (20%)	31/73	41/79	16.4	11.3	0.682 (0.413–1.123)
	Positive (60%)	25/50	31/55	11.9	11.1	0.683 (0.381–1.224)

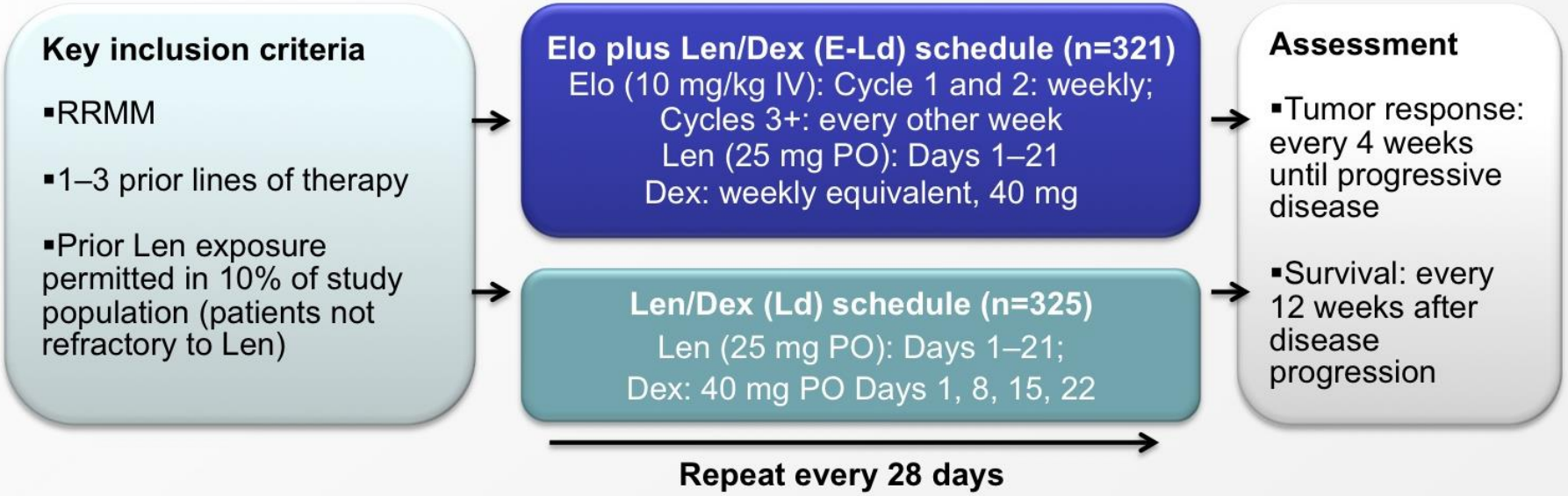


*del(17p) subgroup includes patients with del(17p) alone or in combination with t(4;14) or t(14;16)

Avet-Loiseau H, *et al.* Blood 2017

ELOQUENT-2: ELOTUZUMAB, Revlimid and Dexamethasone (ERd) vs Revlimid and Dexamethasone (Rd) in RRMM

Elotuzumab is approved by FDA and EMA in combination with len-dex for patients who have received at least 1 prior lines of therapy



- Open-label, international, randomized, multicenter, **phase 3 trial** (168 global sites)
- **646 pts**
- Median n° treatment cycles Elo Ld: 19 (1-42)
- 83% pts received more than 90% dose intensity

Lonial S et al, NEJM 2015

ELOQUENT-2: PFS BY CYTOGENETIC RISK STATUS AT BASELINE

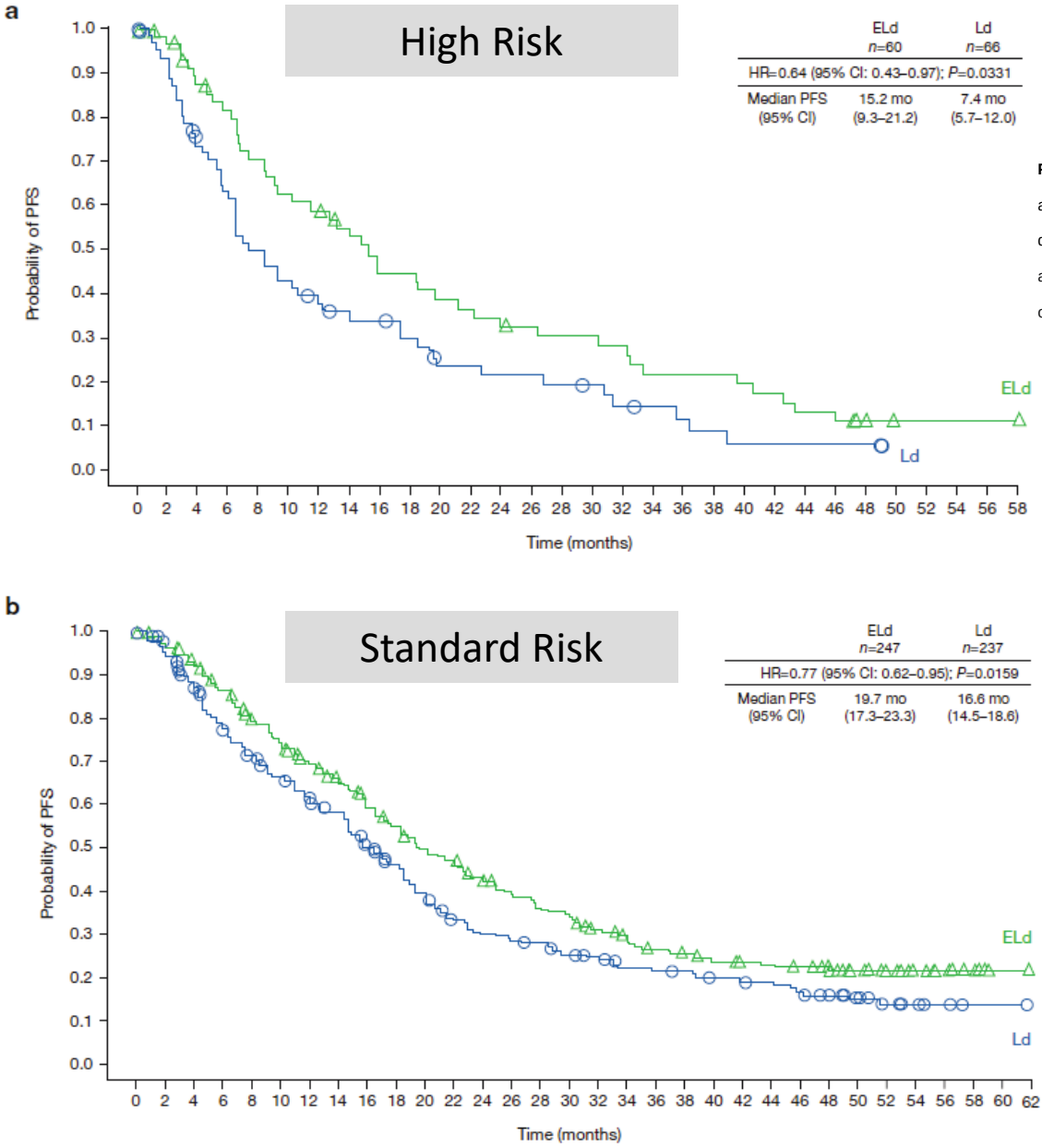
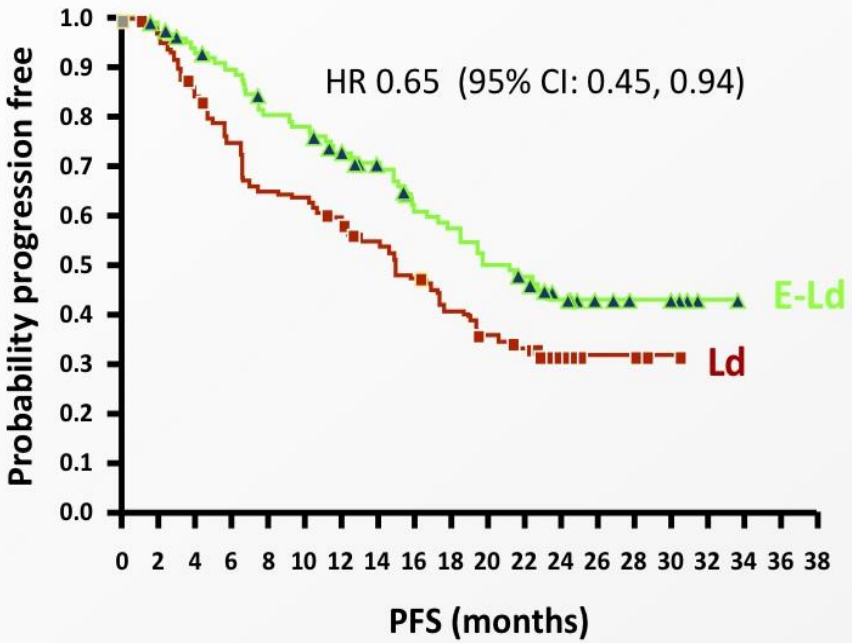


Figure S1. Kaplan–Meier curves of PFS for (**a**) high-risk and (**b**) standard-risk patients according to IMWG risk definition. High risk was defined as ISS stage II or III and t(4;14) or del(17p) abnormality; low risk as ISS stage I or II and the absence of t(4;14), del(17p) and 1q21 abnormalities, and age <55 years; and standard risk as not meeting either the definition of high or low risk.

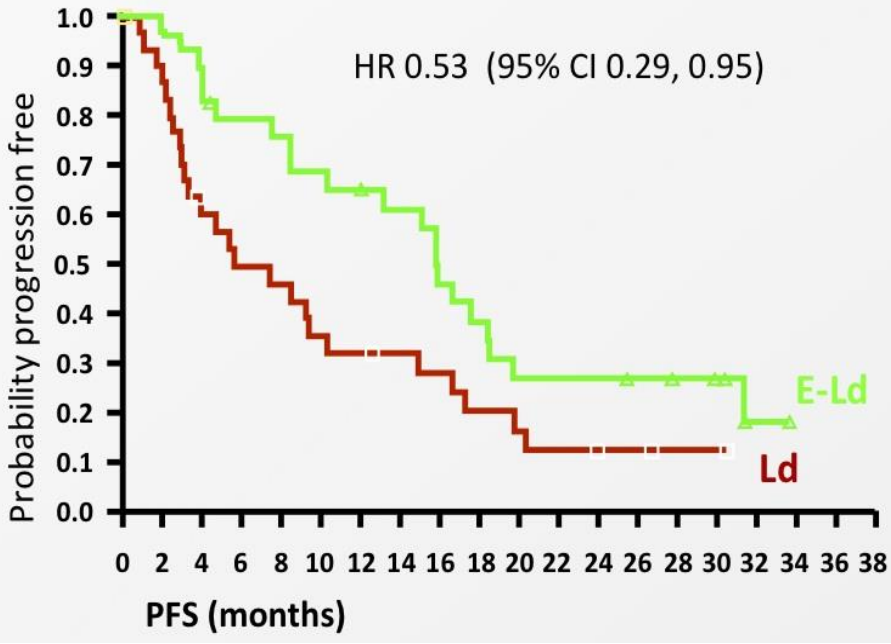
Dimopoulos MA *et al* Cancer 2018

ELOQUENT-2: PFS in del(17p) and t(4;14)

Del(17p)+



Del(4;14)+



E-Ld: median (95% CI): 21.19 (16.62, NE)
Ld: median (95% CI): 14.92 (10.61, 18.50)

E-Ld: median (95% CI): 15.84 (8.41, 18.46)
Ld: median (95% CI): 5.55 (3.09, 10.25)

Elo-Rd del(17p) negativity: median (95% CI): 18.46 (15.84, 22.77)

ERd improves the outcome of patients with high risk CA in comparison with Rd
High risk defined by: t(4;14) or t(14;16) or with del(17p) in ≥1% of PCs

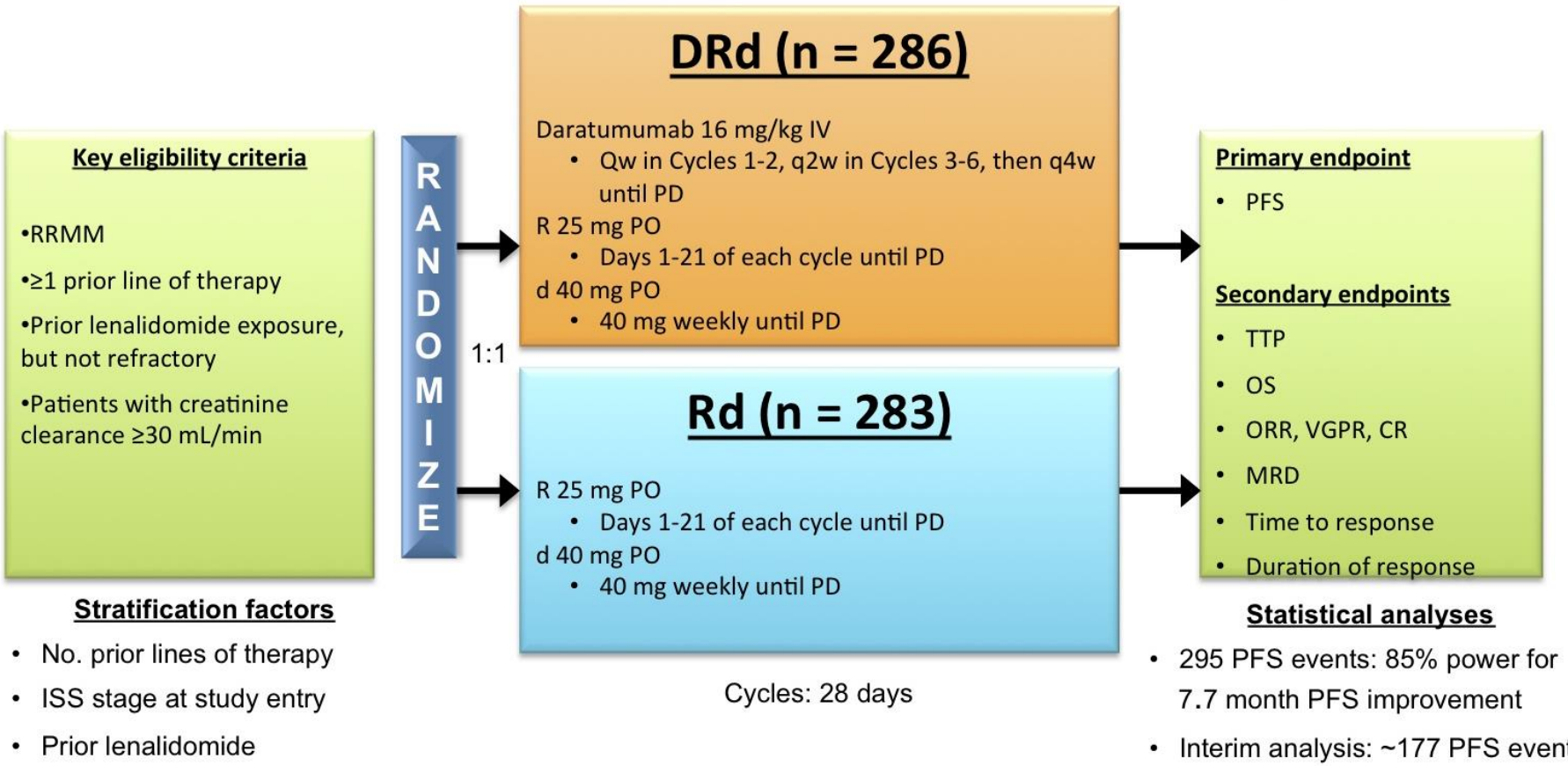
Moreau P, et al. *Blood*. 2015;126: Abstract 727.

Dimopoulos M et al, ASH 2015
Lonial S et al, NEJM 2015

POLLUX: Daratumumab, Revlimid and Dexamethasone (DRd) vs Revlimid and Dexamethasone (Rd) in RRMM

Daratumumab is approved by FDA in combination with len-dex for pts who have received at least 1 prior line of therapy

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study



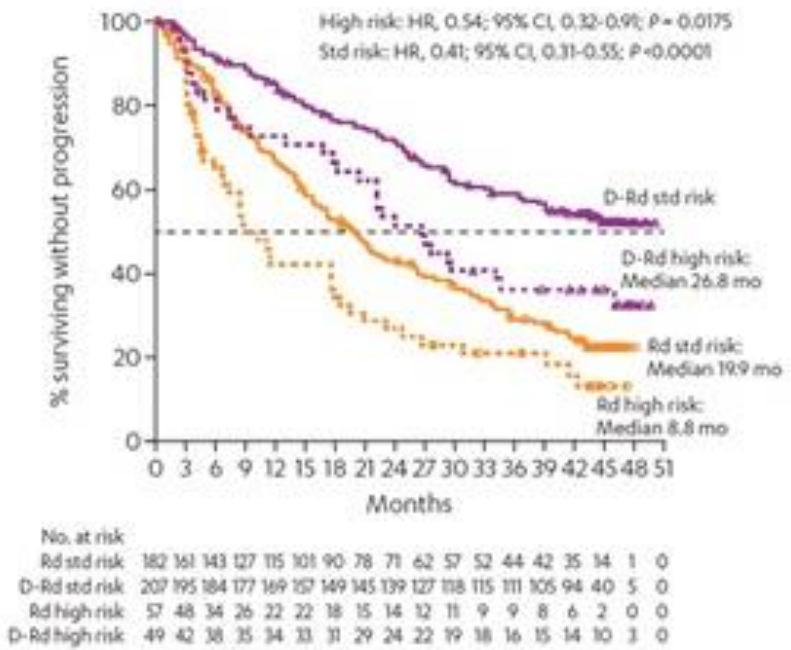
Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

Dimopoulos MA et al, N Engl J Med. 2016;375(14):1319-1331

POLLUX: PFS UPDATE BY CYTOGENETIC RISK STATUS (NGS AND FISH KARYOTIPING COMBINED)

Standard risk: HR 0.41 median PFS NR vs 19.9
High risk: HR 0.54 median PFS 26.8 vs 8.8

D-Rd prolonged PFS vs Rd among patients of high-risk or standard-risk cytogenetic status



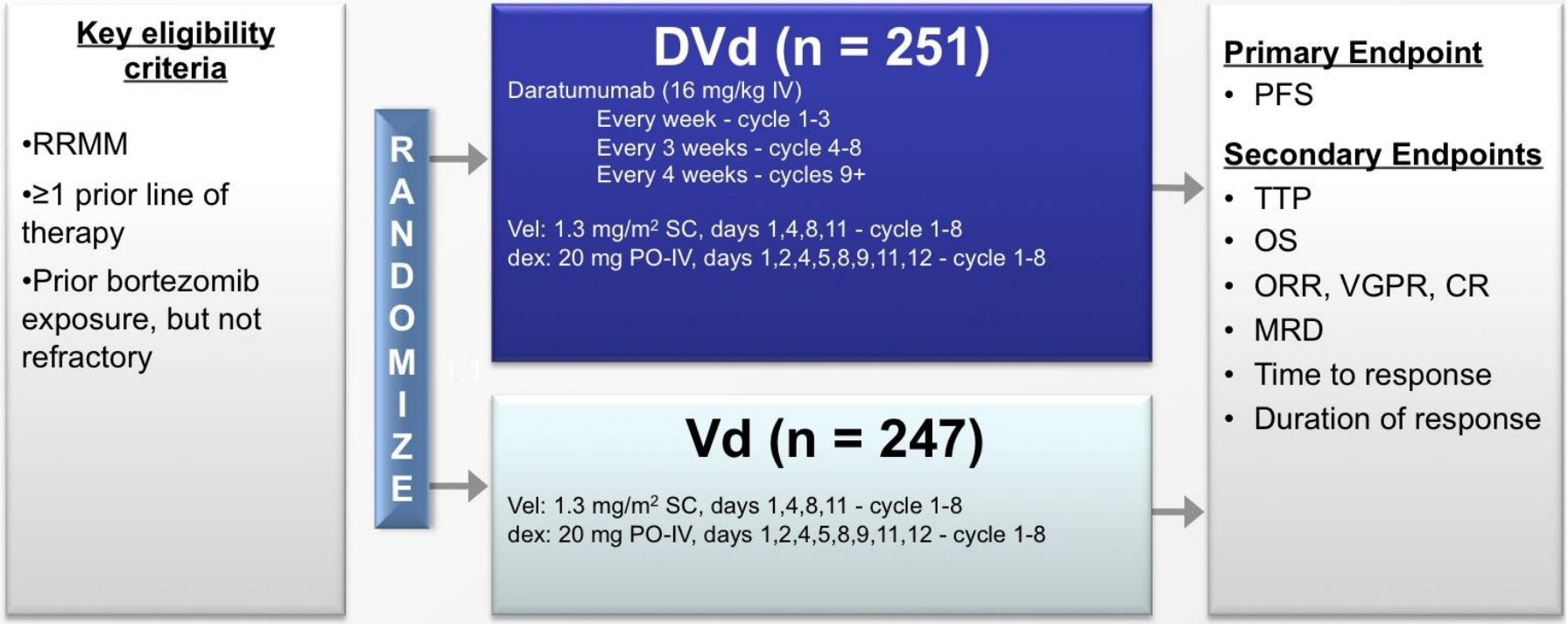
PFS, progression-free survival; D-Rd, daratumumab/lenalidomide/dexamethasone; CI, confidence interval; Rd, lenalidomide/dexamethasone; HR, hazard ratio; std, standard.

Bahlis et al., ASH 2018; abstract 1996

CASTOR: Daratumumab, Velcade and Dexamethasone (DVd) vs Velcade Dexamethasone (Vd) in RRMM

Daratumumab is approved by FDA in combination with btz-dex for pts who have received at least 1 prior line of therapy

Multicenter, randomized, open-label, active-controlled phase 3 study



- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

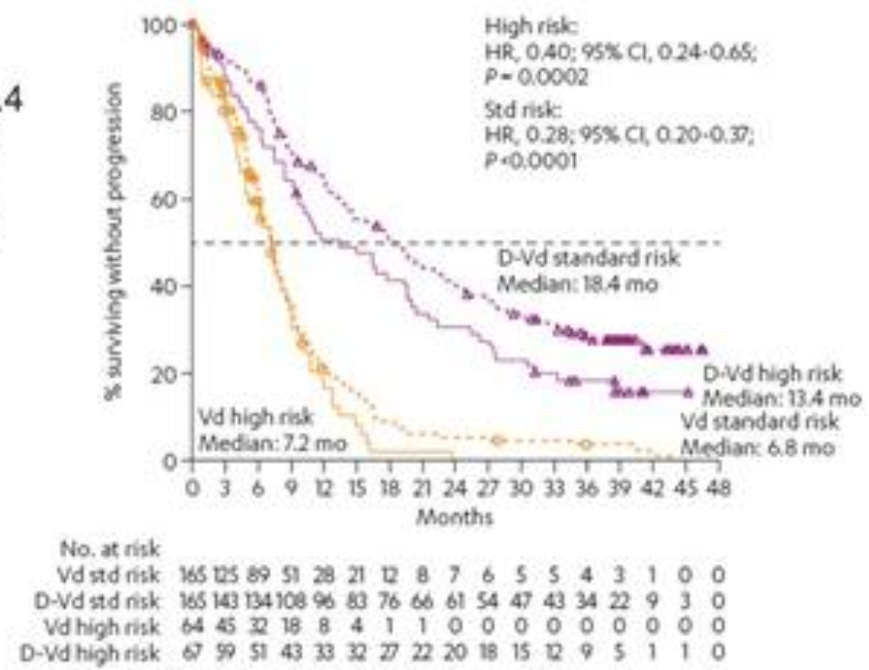
Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

Palumbo A et al. N Engl J Med 2016;375:754-66

CASTOR: PFS UPDATE BY CYTOGENETIC RISK STATUS

Standard risk: HR 0.28 median PFS 18.4 vs 6.8
High risk: HR 0.40 median PFS 13.4 vs 7.2

- The PFS benefit for D-Vd vs Vd was maintained in patients with high (median: 13.4 vs 7.2 months; HR, 0.40; 95% CI, 0.24-0.65; P<0.001) and standard cytogenetic risk (median: 18.4 vs 6.8 months; HR, 0.28; 95% CI, 0.20-0.37; P<0.0001)



PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; D-Vd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; std, standard.

Mateos et al., ASH 2018; abstract 3270

ENDEAVOR: Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd) in RRMM

Carfilzomib is approved by FDA and EMA in combination with dex for pts who have received at least 1 prior line of therapy

Randomization 1:1

N=929

Stratification:

- **Prior proteasome inhibitor therapy**
- **Prior lines of treatment**
- **ISS stage**
- **Route of V administration**

Kd

Carfilzomib 56 mg/m² IV

Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)

Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg

Days 1, 2, 8, 9, 15, 16, 22, 23

28-day cycles until PD or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m² (IV bolus or subcutaneous injection)

Days 1, 4, 8, 11

Dexamethasone 20 mg

Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles until PD or unacceptable toxicity

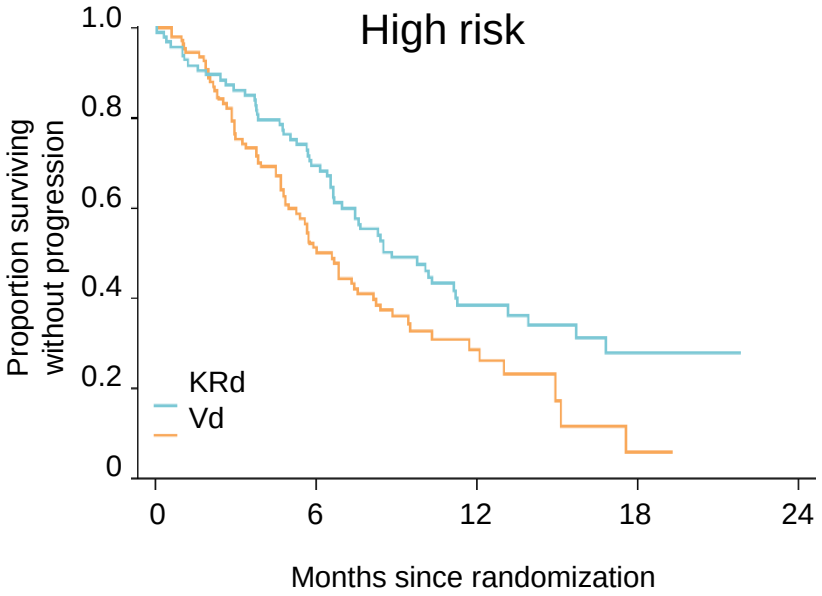
Primary endpoint: PFS

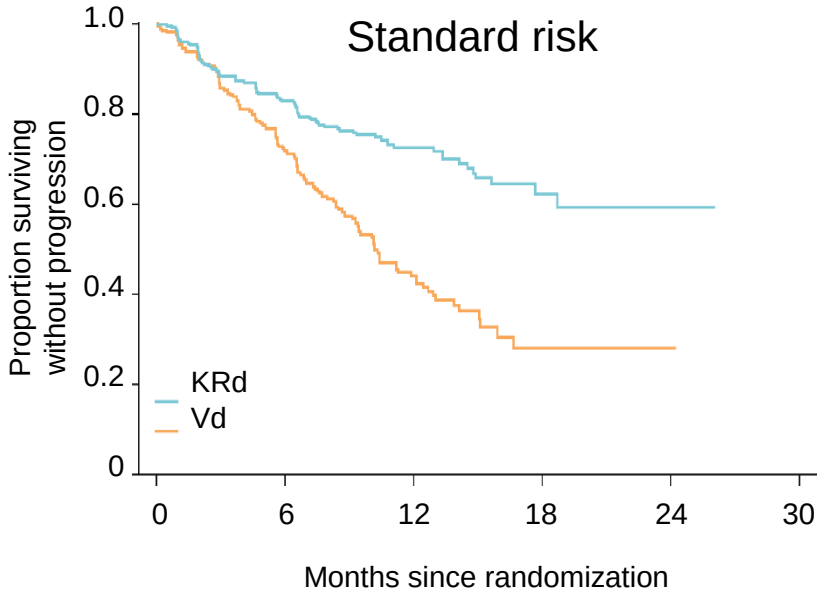
- 1–3 prior treatments, not Carf or Bort refractory

(54% bort exposed, 38% lena exposed)

Dimopoulos D et al, Lancet Oncology 2016

ENDEAVOR: PFS BY CYTOGENETIC RISK STATUS AT BASELINE





	Kd (n=97)	Vd (n=113)
PFS, median months (95% CI)	**8.8 (6.9–11.3)**	**6.0 (4.9–8.1)**
HR (95% CI)	**0.646 (0.453–0.921)**	

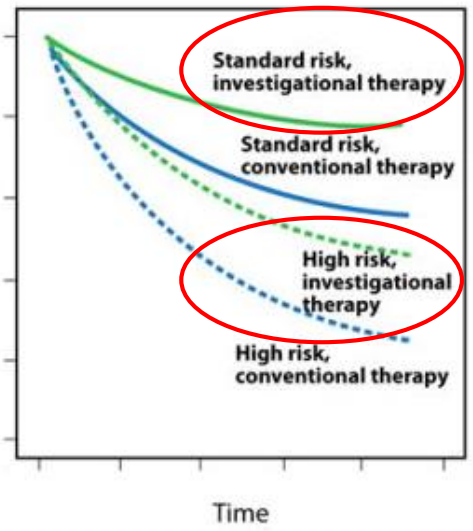
NE, not estimable

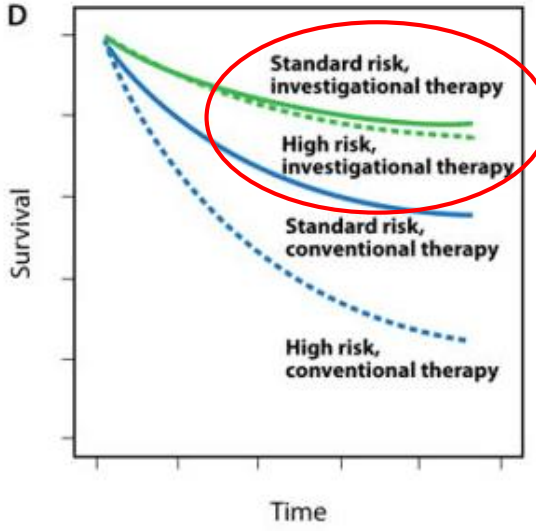
	Kd (n=284)	Vd (n=291)
PFS, median months (95% CI)	**NE (18.7–NE)**	**10.2 (9.3–12.2)**
HR (95% CI)	**0.439 (0.333–0.578)**	

Chang WJ, *et al.* Leukemia 2017

SAMPLE KAPLAN-MEIER SURVIVAL CURVES

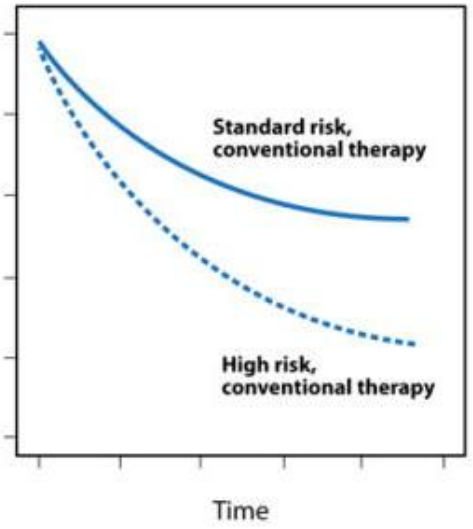
Improved survival in high-risk patients receiving novel therapy, but still inferior to that of standard-risk patients receiving novel therapy.

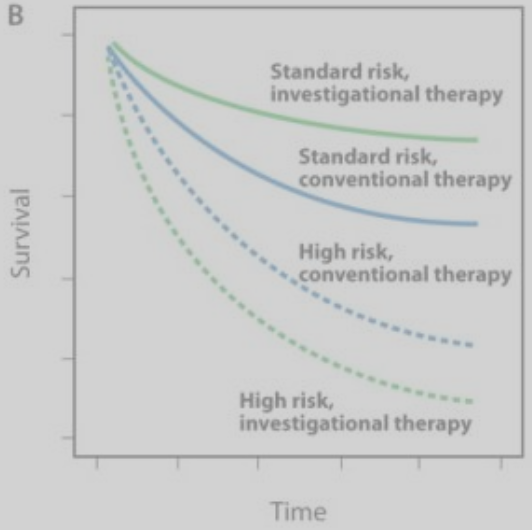




High-risk status is overcome with novel therapy, and these patients now have survival equivalent to that of standard-risk patients.

Inferior survival based on current high-risk molecular abnormalities.





Worsened survival in high-risk patients receiving novel therapy.

Lancman G *et al* Clin Adv Hematol Oncol. 2017

PFS IN PATIENTS WITH HIGH RISK CAs IN RRMM

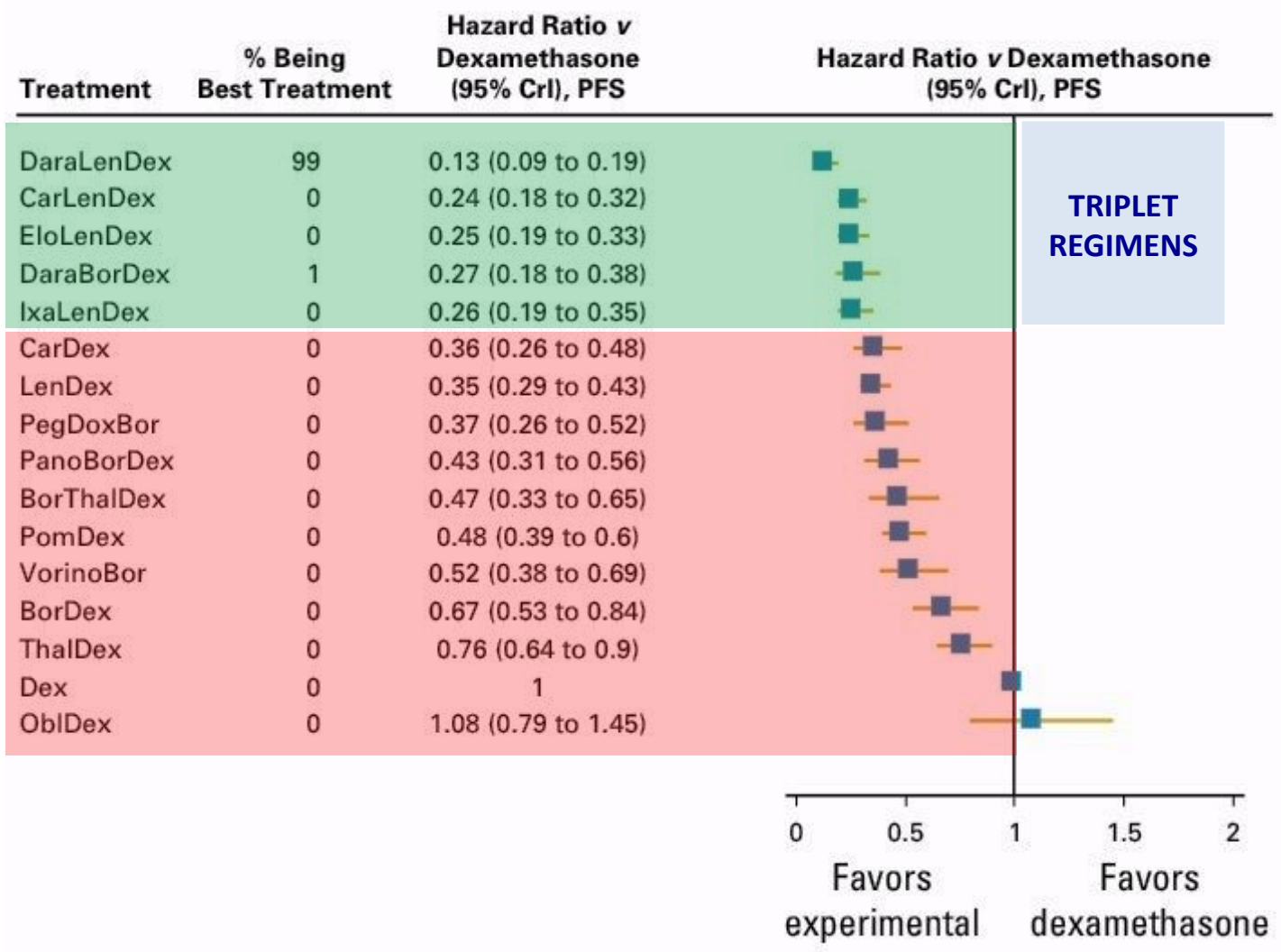
Regimen	Definition of High Risk	All high risk	Del (17p)	t (4;14)
KRd vs Rd **Aspire**	t(4;14) or t(14;16) or 60% del(17p)	23.1 vs 13.9 mo (HR 0.70)	24.5 vs 11.1 mo (HR NA)	23.1 vs 16.7 mo (HR NA)
IRd vs Rd **Tourmaline MM1**	t(4;14) or t(14;16) or 5% del(17p)	21.4 vs 9.7 mo (HR 0.543)	21.4 vs 9.7 mo (HR 0.596)	18.5 vs 12 mo (HR 0.645)
Elo-Rd vs Rd **Eloquent 2**	t(4;14) or del(17p)	15.2 vs 7.4 mo (HR 0.64)	21.2 vs 14.9 (HR 0.65)	15.8 vs 5.5 (HR 0.53)
DRd vs Rd **Pollux**	t(4;14) or t(14;16) or 50% del(17p)	26.8 vs 8.8 mo (HR 0.54)	NA	NA
DVd vs Vd **Castor**	t(4;14) or t(14;16) or 50% del(17p)	13.4 vs 7.2 mo (HR 0.40)	NA	NA
Kd vs Vd **Endeavor**	t(4;14) or t(14;16) or 20% del(17p)	8.8 vs 6.0 mo (HR 0.646)	7.6 vs 4.9 mo (HR NA)	10.1 vs 6.8 mo (HR NA)

PHASE 3 STUDIES IN RRMM: CLINICAL PRACTICE IN HR CAs

TRIAL NAME	TREATMENT	EFFICACY
ASPIRE	Carfilzomib, Revlimid and Dex (KRd) vs Revlimid and Dex (Rd)	Improve but not completely overcome prognosis of Pts with HR CAs (≥ 60% PCs positive)
TOURMALINE-MM1	Ixazomib, Revlimid and Dex (IRd) vs Revlimid and Dex (Rd)	Overcome del(17p) (≥20 PCs positive) and improve t(4;14) prognosis of Pts with CAs
ELOQUENT-2	Elotuzumab, Revlimid and Dex (EloRd) vs Revlimid and Dex (Rd)	Improve t(4;14) and overcome del(17p) prognosis of Pts with CAs (≥ 1% PCs positive)
POLLUX	Daratumumab, Revlimid and Dex (DaraRd) vs Revlimid and Dex (Rd)	Improve but not overcome prognosis of Pts with HR CAs (≥ 50% PCs positive)
CASTOR	Daratumumab, Velcade and Dex (DaraVd) vs Velcade and Dex (Vd)	Improve but not overcome prognosis of Pts with CAs (≥ 50% PCs positive)
ENDEAVOR 	Carfilzomib and Dex (Kd) vs Bortezomib and Dex (Vd)	No good option in Pts with HR CAs

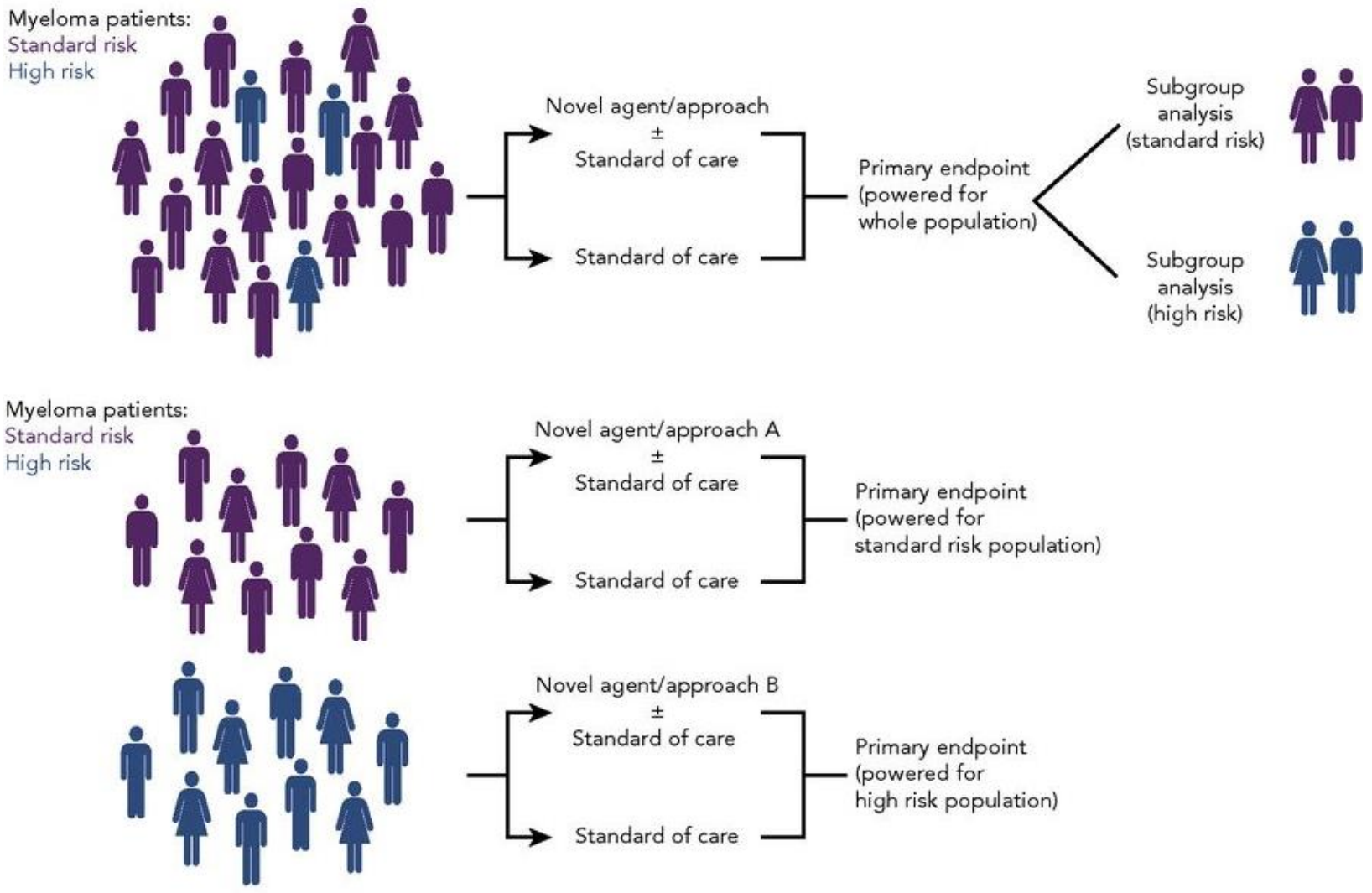
CAs: Cytogenetic Abnormalities; **PCs**: Plasma cells; **HR**: High Risk; **Pts**: Patients.

NETWORK META-ANALYSIS: TREATMENT OUTCOMES IN RRMM



van Beurden-Tan *et al* J Clin Oncol 2017

Clinical Trial Design Strategies for Personalized Treatment in Myeloma



Adapted from Pawlin C and Davies FE Blood 2018

NEW WORLD OF RRMM IN 2017

(Adapted from ESMO Guidelines, Moreau *et al.* Ann Oncol 2017)

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT/Rd

FIRST RELAPSE

Second Transplant

after Bortezomib-based induction: **combo based on Revlimid**	**after IMID-based induction:** **combo based on Bortezomib**
Rd, RCd, KRd, Elo-Rd,Ixa-Rd, Dara-Rd	Vd, VCd, Elo-Vd, Dara-Vd, Pano-Vd, Kd

SECOND RELAPSE

Rd, KRd, Elo-Rd, Ixa-Rd, Dara-Rd | Kd | Vd, Elo-Vd, Dara-Vd

Pomalidomide-Dexamethasone-Cyclo

Daratumumab Single Agent or Combination

Clinical trials (MoAbs, check-point inhibitors, venetoclax, selinexor, anti BCMA…)

PHASE 3 TRIALS IN RRMM: CONVENIENCE

REGIMENS	ROUTE OF ADMINISTRATION	DOSING SCHEDULE	HOSPITAL VISIT	ADMINISTRATION TIME
KRd ASPIRE	IV	Cycle 1-12: Days 1,2,8,9,15 and 16 of 28-day cycle Cycle 13-18: Days 1,2,15 and 16 of 28-day cycle	**Twice a week (3-week-on/1-week-off)**	Overs 30 min + pretreatment hydratation
Kd ENDEAVOR	IV	Carfilzomib: days 1,2,8,9,15 and 16 of 28- day cycle	**Twice a week (3-week-on/1-week-off)**	Overs 30 min + pretreatment hydratation
DaraVd CASTOR	IV (+ Bortezomib SC)	Daratumumab: days 1,8 and 15 of 21-day cycle 1 to 3, Q3W for cycle 4 to 8 then Q4W Bortezomib: days 1,4,8 and 11	**4 to 5 visits by 21-day cycle**	6.5 hours for the first infusion and 3.5 hours for subsequent infusions. Need premedicaton
DaraRd POLLUX	IV	Days 1,8,15 and 22 of 28-day cycle 1 and 2, days Q2W for cycle 3 to 6 then Q4W thereafter	**QW for 8 weeks, Q2W for 16 weeks, then Q4W**	6.5 hours for the first infusion and 3.5 hours for subsequent infusions. Need premedicaton
EloRd ELOQUENT-2	IV	Days 1,8,15 and 22 of 28-day cycle 1 and 2, then days 1 and 15 cycle 3+	**QW for 8 weeks then Q2W**	3 hours for the first infusion 1,5-1 hour for subsequent infusions. Need premedication
IxaRd TOURMALINE-MM1	PO	Days 1,8,15 of 28-day cycle	**Q4W**	0 hours

Modified from Moreau P. Blood 2017

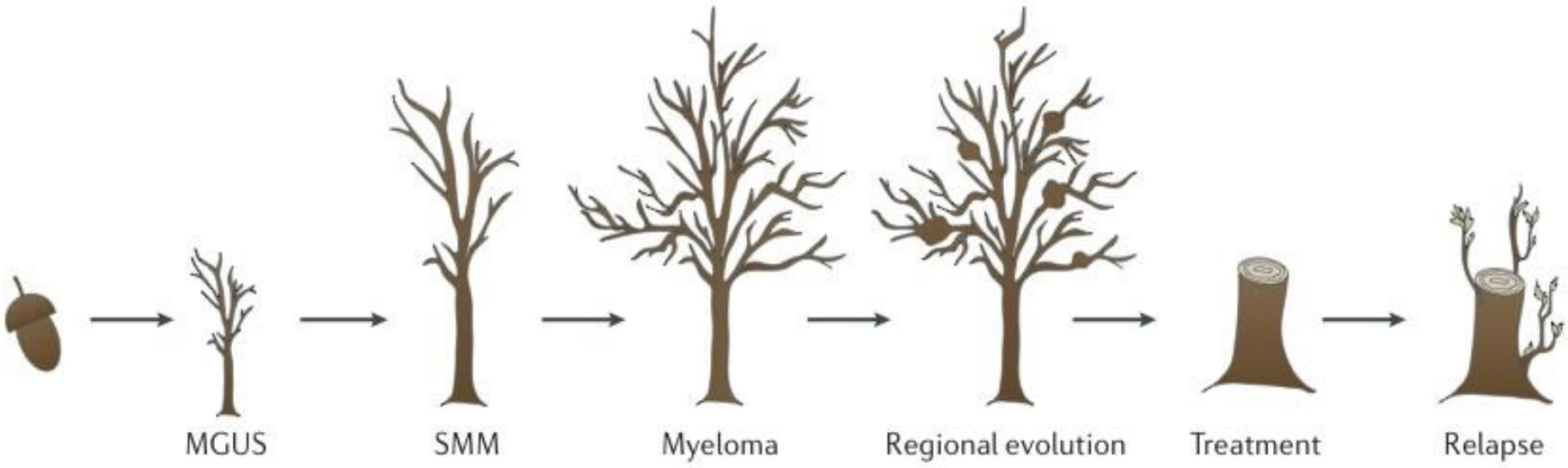
CONCLUSIONS - 1

- Major advances have occurred in the therapy of multiple myeloma with several new classes of agents approved.
- Triplet regimens are better than doublet in terms of response rate, PFS, and seem to be superior in OS in RRMM.
- Similarity but also differences in between studies (previous drugs exposure/refractoriness, cytogenetic high-risk cut off).

CONCLUSIONS - 2

- Restaging of myeloma and evaluation for disease evolution is important at the time of relapse.
- No treatment regimen showed to consistently improve outcomes in high risk MM
- Although MM guidelines both recognize CAs as prognostic factors, neither provides categorized treatment recommendations for patients with high risk CAs
- Future risk stratified treatments (cytogenetics)

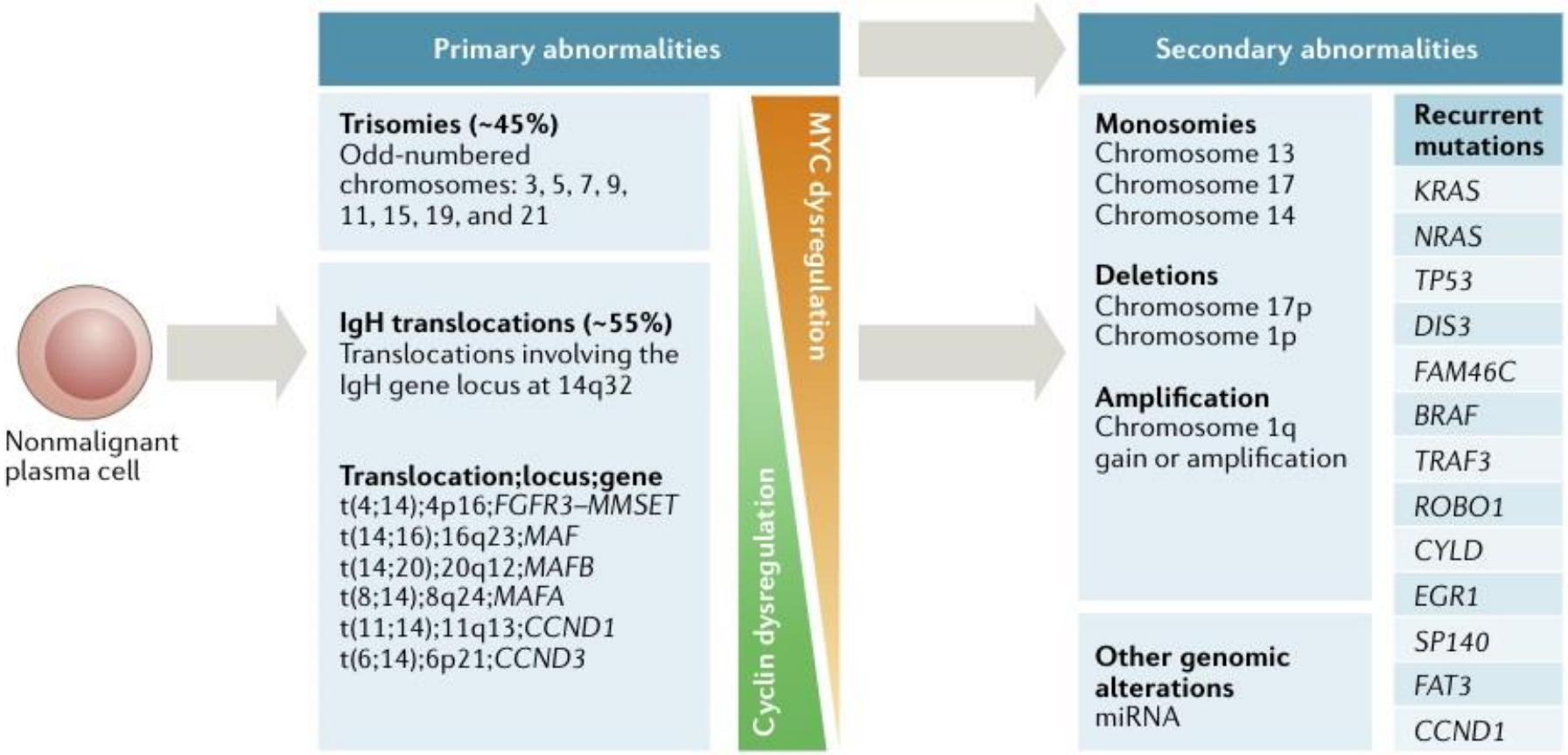
GRAZIE PER L'ATTENZIONE



Pawlyn C and Morgan GJ Nature Reviews Cancer 2017

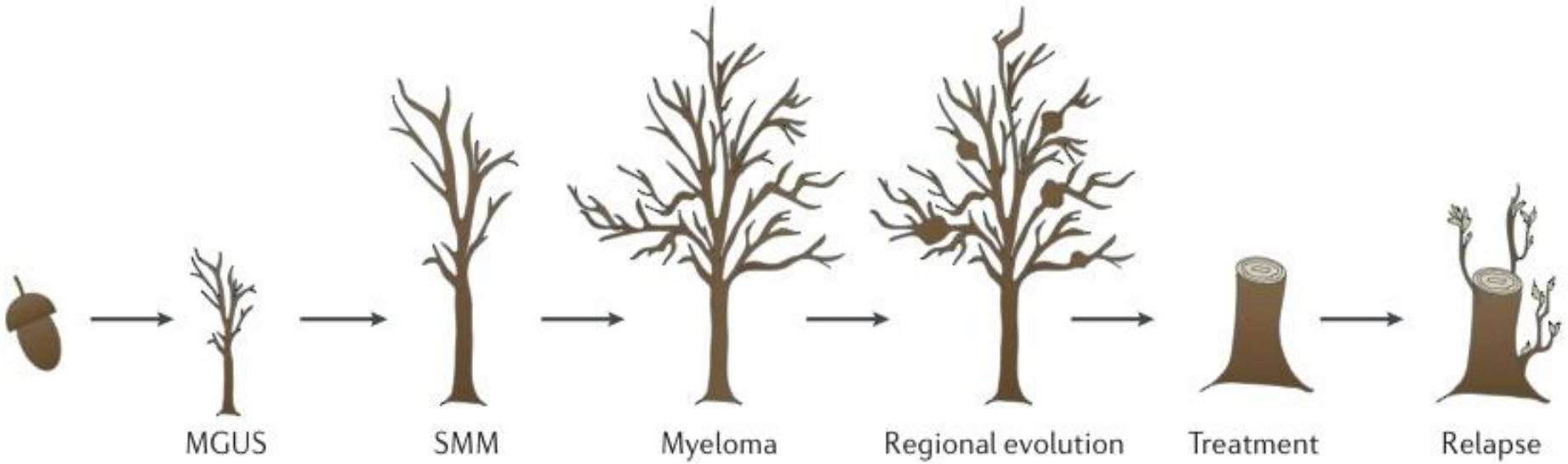
BACK UP

PRIMARY and SECONDARY CYTOGENETIC ABNORMALITIES



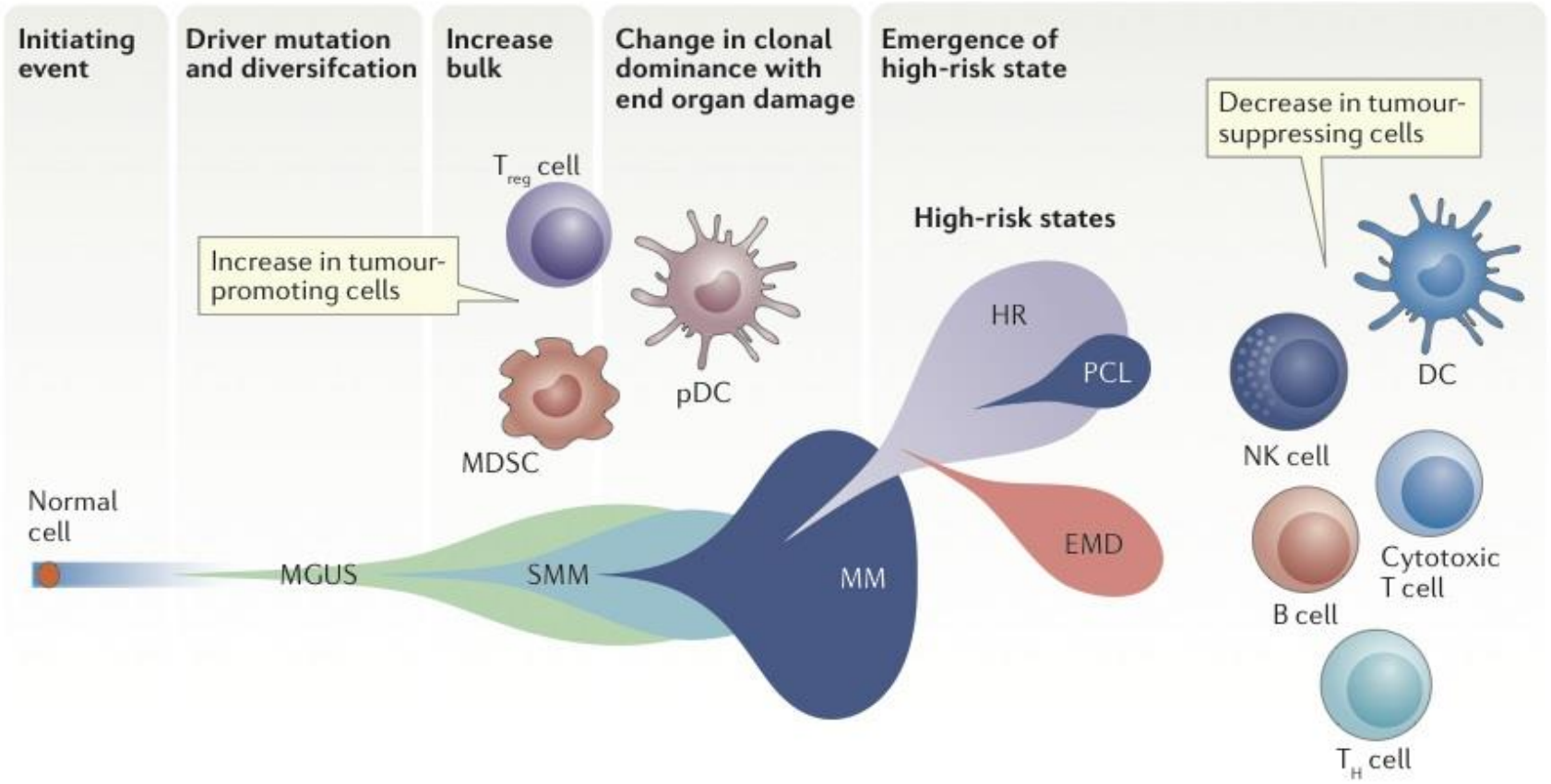
Shaji K. Kumar * and S. Vincent Rajkumar*

THE EMERGENCE of TREATMENT RESISTANT SUB-CLONES is a KEY FEATURE of RELAPSE in MULTIPLE MYELOMA



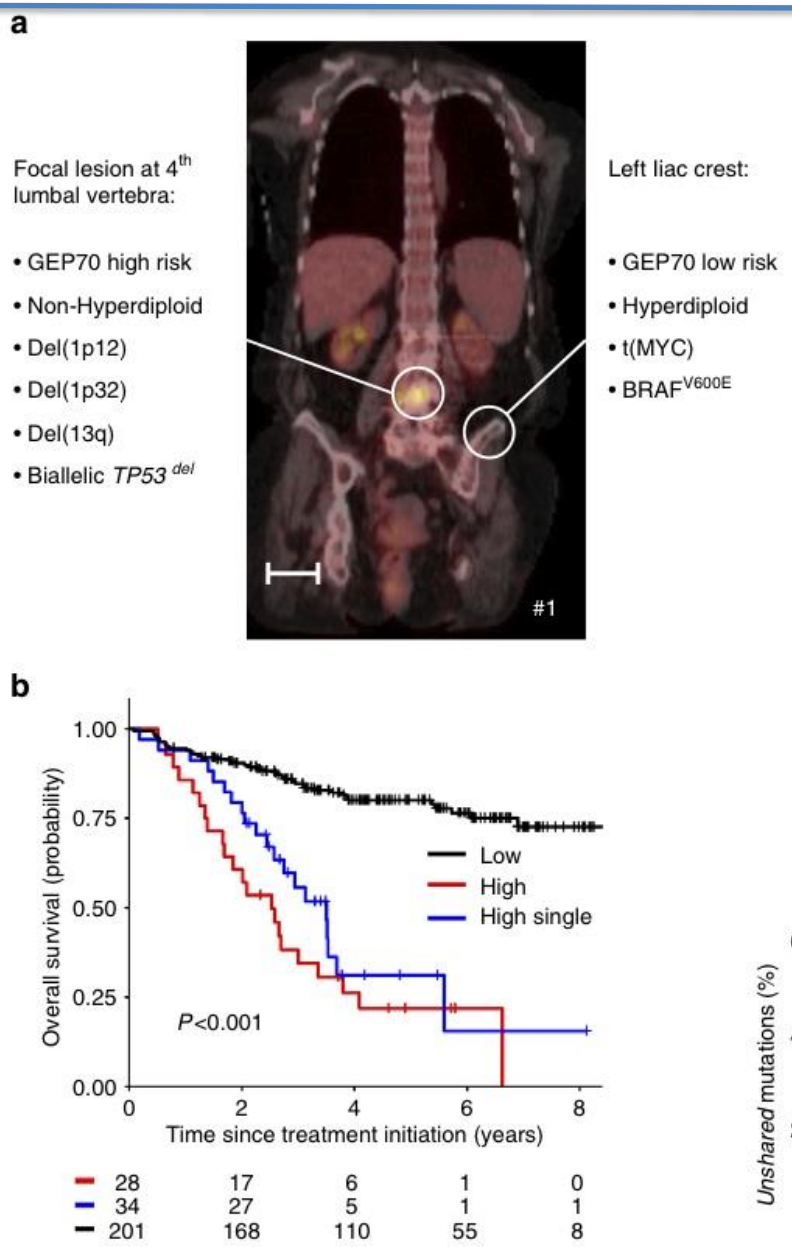
Pawlyn C and Morgan GJ Nature Reviews Cancer 2017

THE INTERACTION BETWEEN GENETIC DRIVERS and MICROENVIRONMENT CHANGES DRIVES HIGH-RISK DISEASE STATES



Pawlyn C and Morgan GJ Nature Reviews Cancer 2017

SPATIAL GENOMIC ETEROGENEITY in MULTIPLE MYELOMA



Rasche L *et al* Nature Comm 2017

REVISED ISS STAGING SYSTEM

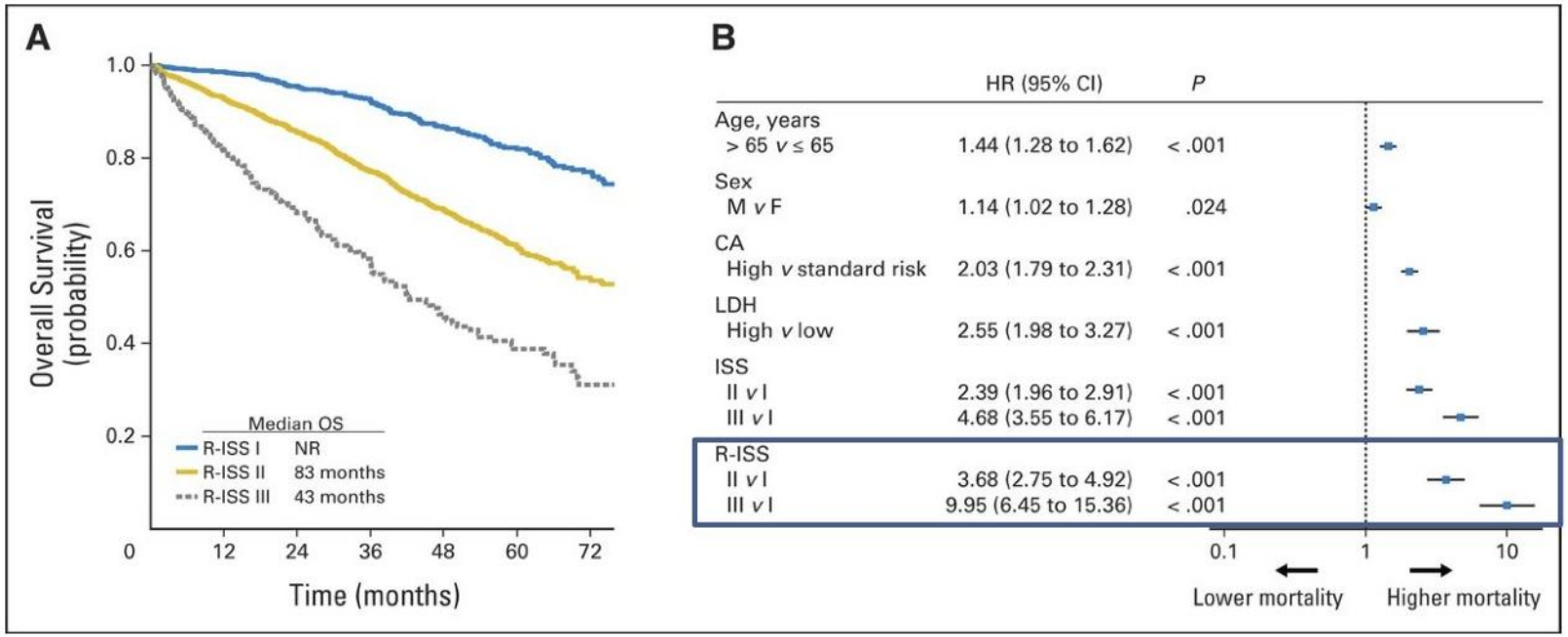
A total of **3,060 pts** with **NDMM** enrolled onto 11 international, multicenter clinical trials
All patients received new drugs (IMIDs or PIs)

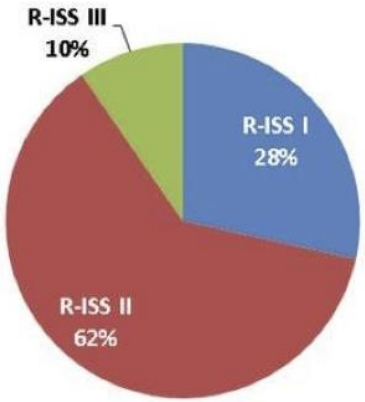
Prognostic factor		Criteria
ISS stage	I	Serum β_2-microglobulin < 3.5 mg/L; serum albumin ≥ 3.5 g/dL
	II	Not ISS stage I or III
	III	Serum β_2-microglobulin > 5.5 mg/L
CA by iFISH	High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
	Standard risk	No high-risk CA
LDH	Normal	Serum LDH < upper limit of normal
	High	Serum LDH > upper limit of normal
A new model for risk stratification for MM		
R-ISS stage	I	ISS stage I, standard-risk CA by iFISH and normal LDH
	II	Not R-ISS stage I or III
	III	ISS stage III and either high-risk CA by iFISH or high LDH

CA, chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; R-ISS, Revised International Staging System.

Palumbo A *et al* JCO 2015

REVISED ISS STAGING SYSTEM
OVERALL SURVIVAL STRATIFIED by R-ISS ALGORITHM



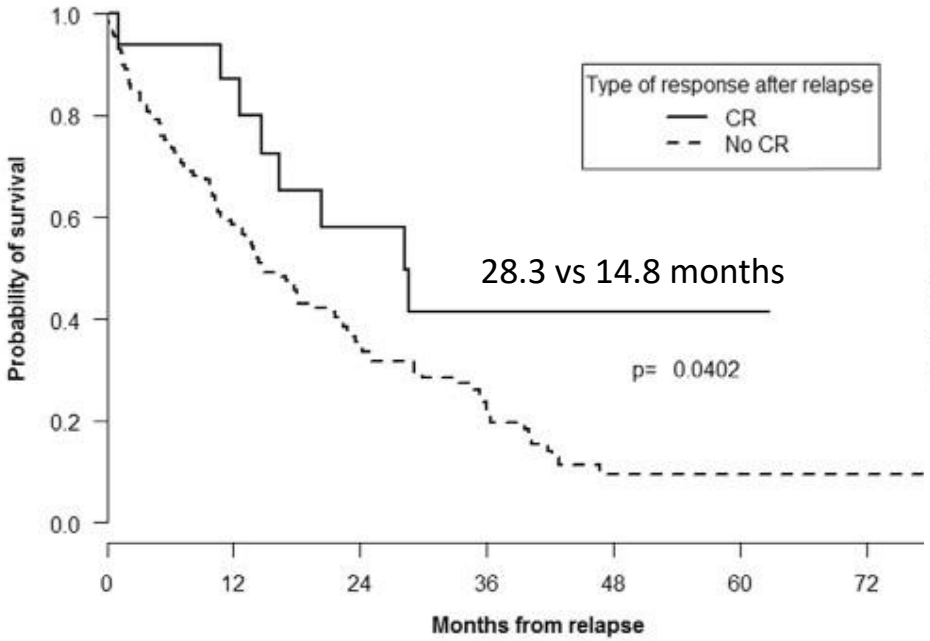


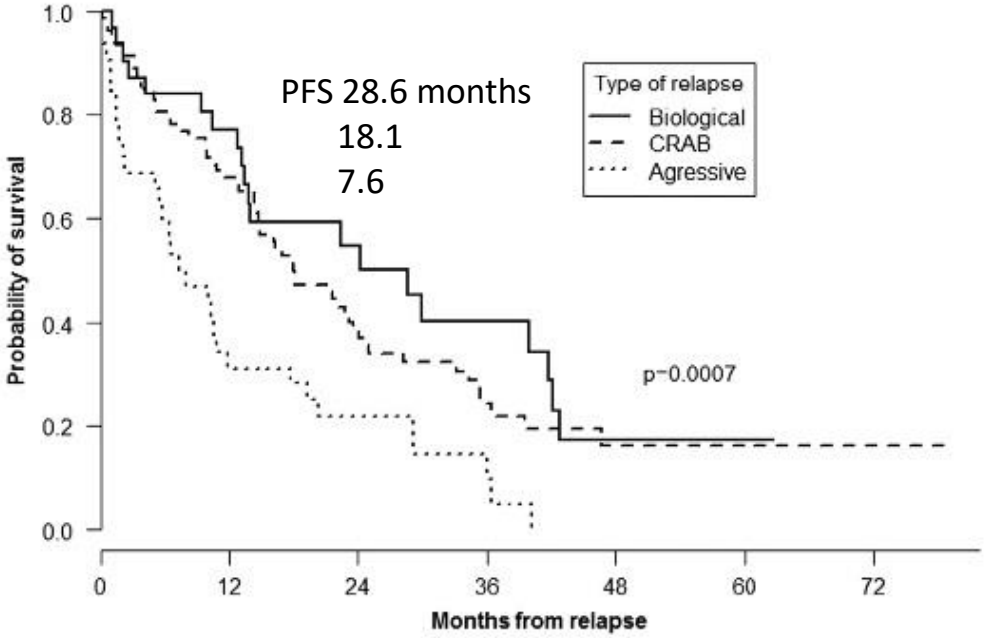
	R-ISS I (N=871)	R-ISS II (n=1894)	R-ISS III (n=295)
5-year PFS, % (n=3060)	54	36	22
5-year OS, %			
All (n=3060)	81	60	40
ASCT (n=1998)	83	62	39
No ASCT (n=1062)	75	52	47

Recent data suggest that R-ISS is predictive in both newly diagnosed MM and RRMM

Palumbo A *et al* JCO 2015

OVERALL SURVIVALL ACCORDING to the TYPE of RESPONSE and RELAPSE





Lopez A *et al.* Leukemia Research Reports 2015

EARLY RELAPSE PREDICTS POOR OUTCOMES

OS from the start of therapy. Kaplan-Meier curve demostrating difference in OS between early and late relapse patients

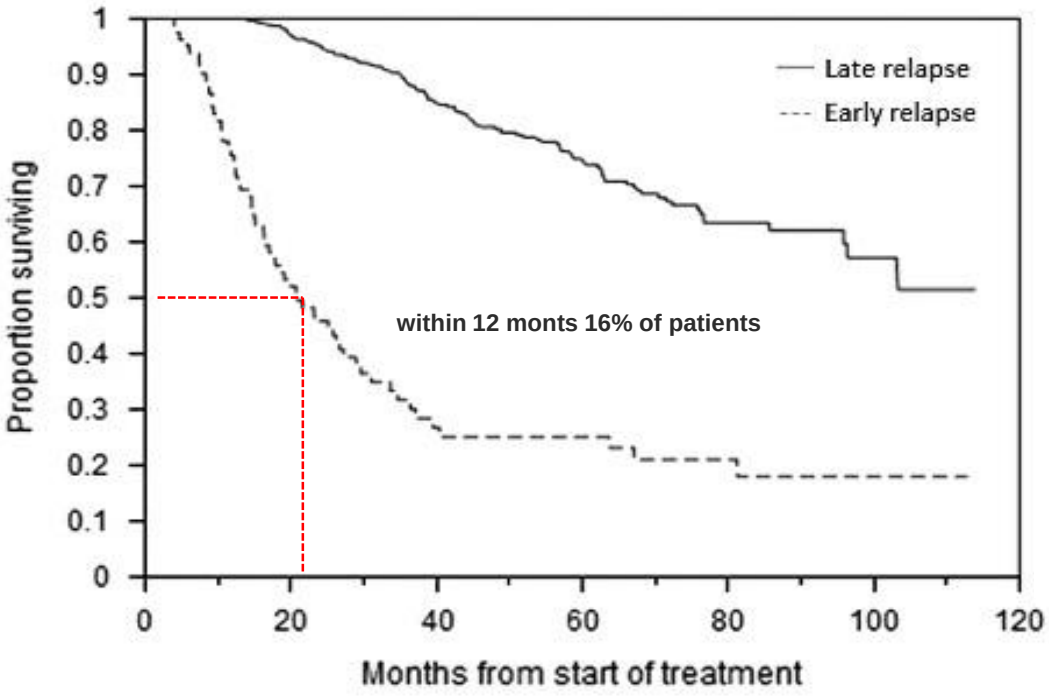


Table 2. Multivariate analyses evaluating predictors of early relapse

Prognostic factor	*Multivariate analysis*	
	HR	P
Male gender	1.8	0.32
Serum albumin <3.5 g/dl	1.6	<0.01
Beta-2 microglobulin >5.5 mg/l	1.5	0.93
Lambda light chain type	1.7	0.23
Serum LDH	1.4	0.76
PCLI at least 3%	1.2	0.07
High-risk FISH	1.7	<0.001

Abbreviations: FISH, fluorescent *in situ* hybridization; HR, hazard ratio; LDH, lactate dehydrogenase; PCLI, plasma cell labeling index.

Majithia N. *et al*. Leukemia 2016

DEFINITIONS OF RELAPSED/REFRACTORY MM

International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma[1]

Primary Refractory myeloma.
It is a disease that is non responsive in patients who have never achieved a minor response with any therapy

Relapsed myeloma.
After a period of being off therapy, it requires the initiation of salvage therapy

Relapsed and refractory myeloma.
It is non responsive while being on salvage therapy (achieved minor response or better at some point in their disease course) or progress within 60 days of last therapy

BIOCHEMICAL RELAPSE: WHEN TO START TREATMENT

It is reasonable to initiate salvage regimens before the development of symptoms, particularly if:

- THERE IS STEEP INCREMENT IN M SPIKE
- **HIGH RISK RELAPSED DISEASE** Table 1. LAUBACH J *et al LEUKEMIA 2016*

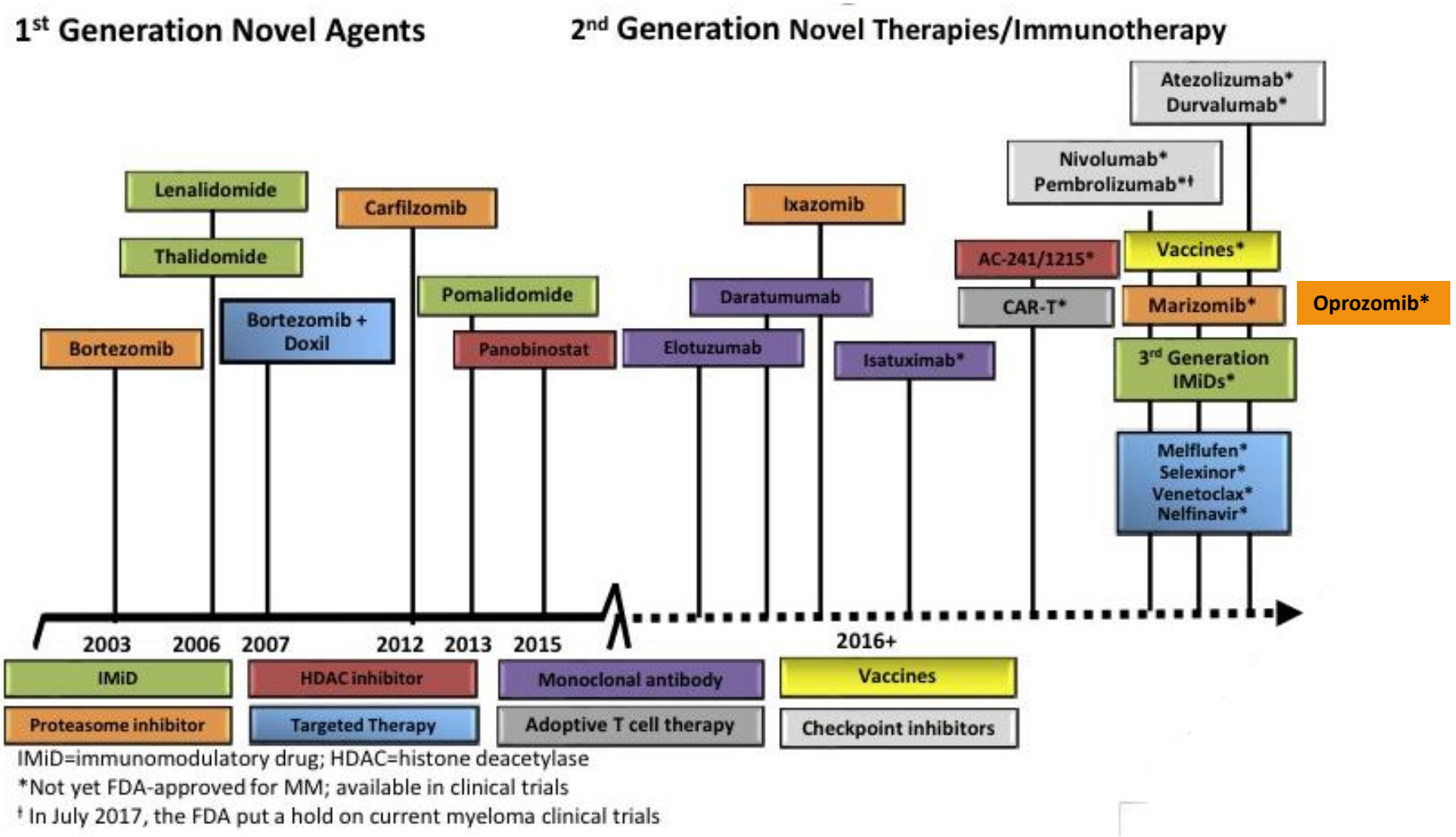
THE DEFINITION OF HIGH-RISK IS ALSO DYNAMIC, CHANGING OVER TIME!

Disease related parameters	
Adverse cytogenetic abnormalities	del(17p), amp(1q21) or t(4;14)
Extramedullary disease	
Short remission duration after first treatment	
ISS stage at relapse	
Isotype transformation	Light chain escape, development of hyposecretory disease
High LDH levels at relapse	

Table 1.

Adapted from Laubach J *et al* Leukemia 2016

CONTINUING EVOLUTION of MM TREATMENT: SELECTED NEW CLASSES and TARGETS 2016-2018



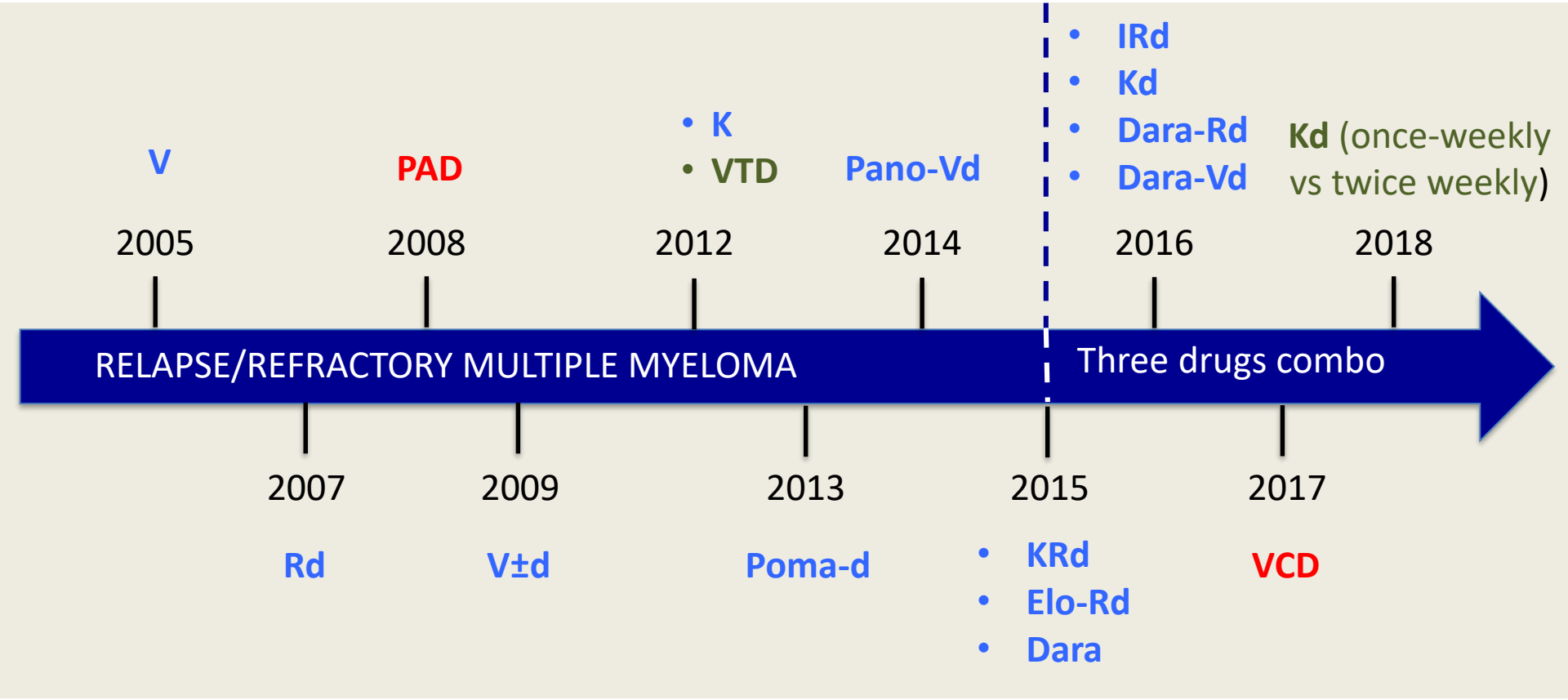
IMiD=immunomodulatory drug; HDAC=histone deacetylase

*Not yet FDA-approved for MM; available in clinical trials

† In July 2017, the FDA put a hold on current myeloma clinical trials

Paul Richardson 2017

TIMELINE of KEY AGENTS and TREATMENT COMBINATIONS that are APPROVED/RECOMMENDED or HAVE INVESTIGATED in PHASE III CLINICAL TRIALS in RRMM



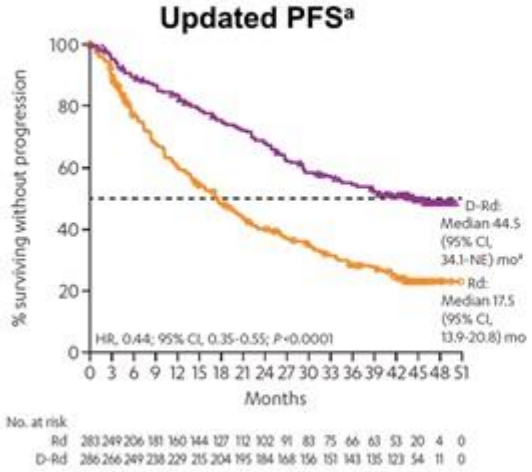
Approved by FDA/EMA

Recommended in current European/US treatment guidelines

Based on clinical trial data

Adapted from Costello C *et al* Future Oncology 2019

Daratumumab + lenalidomide and dexamethasone vs lenalidomide and dexamethasone in RRMM: POLLUX 3-year follow-up



- Median follow-up: 44.3 months
- D-Rd significantly prolonged PFS vs Rd in the ITT population (median: 44.5 months vs 17.5 months; HR, 0.44; 95% CI, 0.35-0.55; P<0.0001)

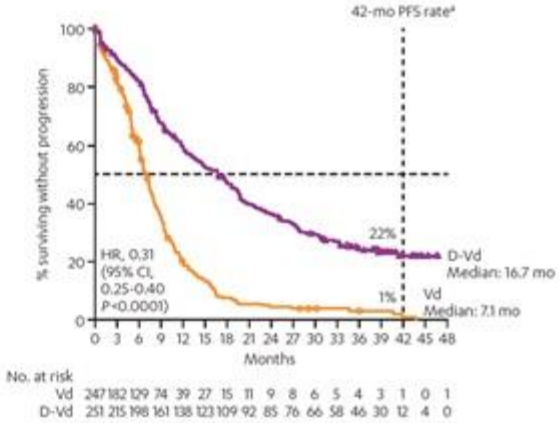
56% reduction in the risk of progression or death in patients receiving D-Rd

[a]The upper bound 95% CI is currently not estimable; median PFS may change with additional follow-up once the upper bound 95% CI estimate is reached.

Bahlis et al., ASH 2018; abstract 1996

Updated PFS in the ITT Population

- Median follow-up: 40.0 months
- PFS was significantly prolonged with D-Vd vs Vd
- PFS benefit was maintained in patients who received 1–3 prior lines of therapy and regardless of cytogenetic risk status
- At time of analysis, 102 deaths in the D-Vd group and 119 deaths in the Vd group were observed; follow-up is ongoing



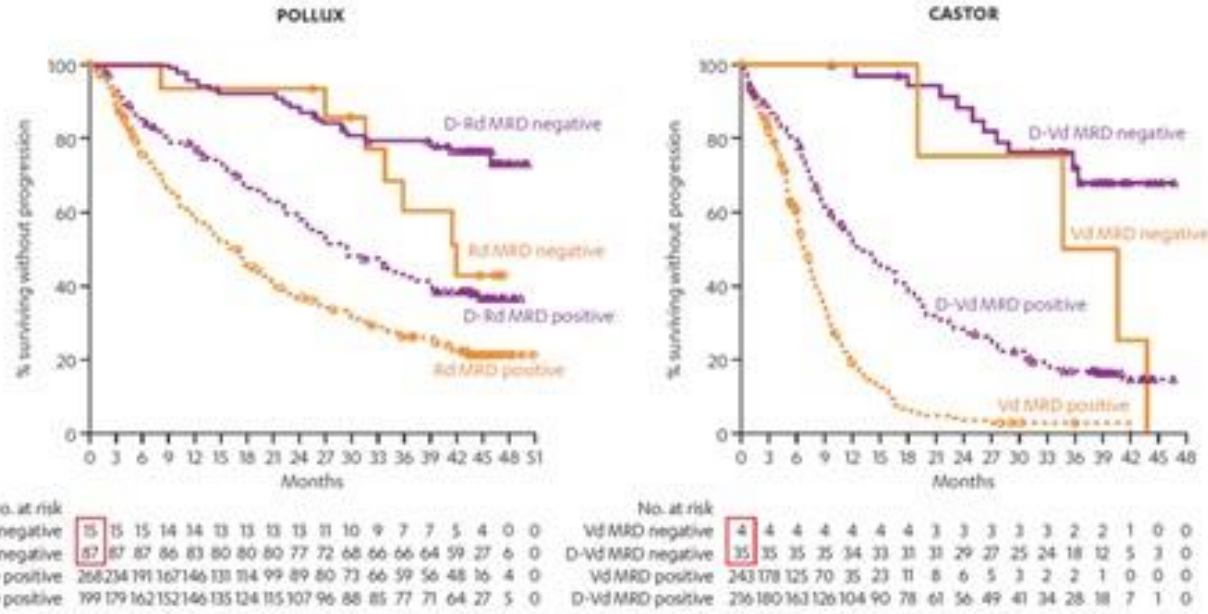
69% reduction in the risk of progression or death in patients receiving D-Vd

PFS, progression-free survival; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval; D-Vd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]Kaplan-Meier estimate.

Mateos et al., ASH 2018; abstract 3270

POLLUX and CASTOR: PFS in high-risk pts by MRD

PFS BASED ON MRD NEGATIVITY IN THE ITT POPULATIONS OF POLLUX AND CASTOR



PFS was prolonged in patients who achieved MRD negativity

PFS, progression-free survival; MRD, minimal residual disease; ITT, intent to treat; Rd, lenalidomide; D-Rd, daratumumab/lenalidomide/dexamethasone; Vd, bortezomib/dexamethasone; D-Vd, daratumumab/bortezomib/dexamethasone.

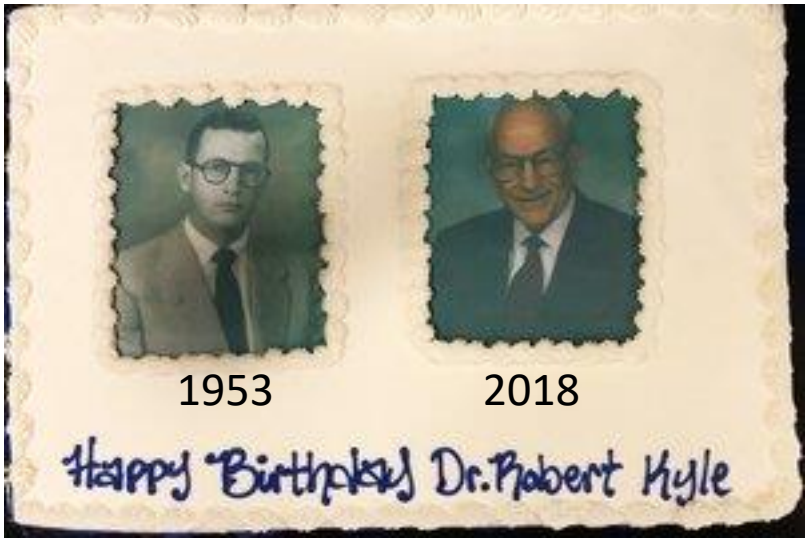
Avet Loiseau et al., ASH 2018; abstract 3272

MAYO CLINIC

mSMART

Mayo Stratification for Myeloma And Risk-adapted Therapy

Relapsed Myeloma



v5 //last reviewed March 2017; Dingli et al. Mayo Clin Proc 2017;92(4):578-59

EMATOLOGIA di VERONA
Policlinico Borgo Roma

< 50 nuovi casi/anno di Mieloma diagnosticati a Verona

< 250 nuovi casi/anno di Mieloma diagnosticati in Veneto

PRIMA VISITA: prenotazione VISITA EMATOLOGICA AMBULATORIALE tramite CUP 045 812 12 12

AMBULATORIO MALATTIE PLASMACELLULARI: LUNEDÌ E GIOVEDÌ – PRENOTAZIONI DOPO PRIMA VISITA EMATOLOGICA

Dichiarazione obbligatoria sui conflitti di interesse

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18, 19 dell'Accordo Stato-Regione del 19 aprile 2012, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

1) Celgene
2) Janssen-Cilag
3) Amgen
4) Takeda
5) BMS

Vittorio Meneghini